The Journal
OF THE KANSAS MEDICAL SOCIETY

Cancer Supplement

Papers Presented at the Third Annual Mid-West

Cancer Conference

WICHITA, KANSAS
Broadview Hotel
January 18, 19, 20, 1951

Supplement, September, 1951 Vol. LII, No. 9

STORMONT MEDICAL LIBRARY
TOPEKA, KANSAS
SEP 24 1951

Entered as second-class matter, May 2, 1914, at the Postoffice at Topeka, Kansas, under the Act of March 3, 1879. Accepted for mailing at special rate of postage provided for in Section 1103, October 13, 1917. Authorized on July 2, 1918.

CANCER SUPPLEMENT

Through this supplemental issue of the Journal of the Kansas Medical Society, the Kansas Division of the American Cancer Society takes pleasure in presenting to the physicians of Kansas the proceedings of its Third Annual Mid-West Cancer Conference, held in Wichita, last January 18, 19, and 20. It follows in general the pattern of its two predecessors of 1949 and 1950.

There are deficiencies in this publication which are due to insurmountable obstacles. First, we have always the difficulty of revising manuscripts of talks to suit them for publication. That is always a problem of some magnitude, for statements or discussions which are entirely appropriate in an address frequently are equally inappropriate for publication. This often requires such extensive revision of recorded transcriptions as to amount to a rewriting of the entire article. Then, too, usually the addresses are profusely illustrated with slides, both black and white, and in color. That these add to the value of such a presentation is not questioned, but it is also recognized that it is not practical to reproduce all slides as used in such a presentation. Hence, the number of illustrations is sharply decreased as the articles are published. In this connection there will be found numerous references to "slides" in the text, when illustrations are not included in the publication. It is hoped that the readers will understand the reasons for these apparent inconsistencies and be tolerant of their omissions. In some cases revisions were going to be so extensive as to require complete rewriting of the transcription and there was not sufficient time on the part of the author to permit doing so within our publication deadline. This has made it necessary to omit or combine some papers which were presented at the meeting.

Due to these and other factors, it will be noted that Dr. Martin's two talks have been combined into one article; that only one of Dr. Pack's talks is reproduced; and that the address presented at the banquet by Dr. Lawrence is not published.

For these unavoidable deficiencies the Kansas Division of the American Cancer Society and the Editorial Board of the Journal of the Kansas Medical Society are genuinely sorry, but we hope and feel that each reader will find that the volume contains much valuable information, and that it will prove to be well worth the effort which has gone into its production. The Kansas Division is genuinely grateful for the courtesies extended by the Editorial Board in making this publication and its distribution possible as a part of its program of professional education in cancer.

GUEST SPEAKERS

Eldridge H. Campbell, Jr., M.D., Albany, New York

Professor of Surgery, Albany Medical College.

Harold W. Dargeon, M.D., New York, New York

Attending Pediatrician, Memorial Hospital; Chairman, Children's Tumor Registry, American Academy of Pediatrics.

Howard T. Karsner, M.D., Washington, D. C.

Medical Research Advisor, Bureau of Medicine and Surgery, United States Navy; Former Professor of Pathology, Western Reserve University, Cleveland, Ohio.

John H. Lawrence, M.D., Berkeley, California

Director and Professor of the Donner Laboratory of Medical Physics, University of California.

Charles L. Martin, M.D., Dallas, Texas

Professor of Radiology, Southwestern Branch of the University of Texas; Director of Martin X-ray and Radium Clinic; Radiological Consultant to Baylor, Parkland and Veterans' Hospitals, Dallas; Prseident, Dallas County Medical Society.

Daniel G. Morton, M.D., Los Angeles, California

Professor of Obstetrics and Gynecology, University of California School of Medicine at Los Angeles.

George T. Pack, M.D., NewYork, New York

Clinical Professor of Surgery, New York Medical College; Attending Surgeon, Memorial Cancer Center.

Danely P. Slaughter, M.D., Chicago, Illinois

Assistant Professor of Surgery, University of Illinois College of Medicine; Director of Tumor Clinic, Research Hospital, Chicago.

Everett D. Sugarbaker, M.D., Jefferson City, Missouri

Director, Sugarbaker Clinic, Jefferson City; Former Director and Chief Surgeon, Ellis Fischel State Cancer Hospital, Columbia, Missouri.

PROGRAM

Thursday, January 18, 1951

Afternoon Session

The Surgical Treatment of Cervical Cancer—Daniel G. Morton, M.D..... Page 5-A
Therapy with Radioactive Isotopes—John H. Lawrence, M.D..... Page 7-A
Cancer and Allied Diseases in Children—Harold W. Dargeon, M.D..... Page 10-A
Surgical Treatment of Advanced Cancer—Everett D. Sugarbaker, M.D... Page 14-A

Friday, January 19, 1951

Morning Session

Congenital Defects and Associated Neoplastic Disorders in Children—
Harold W. Dargeon, M.D. ..... Page 21-A
Carcinoma of the Breast—Everett D. Sugarbaker, M.D..... Page 23-A
Tracer Research and Cancer—John H. Lawrence, M.D..... Page 31-A
The Diagnosis of Accessible Cancer—Danely P. Slaughter, M.D..... Page 35-A

PROGRAM

Friday, January 19, 1951

Afternoon Session

Tumors of the Spine and Spinal Cord With A Discussion of the Diagnostic Significance of Back Pain—Eldridge H. Campbell, M.D..... Page 40-A

The General Pathology of Endocrine Tumors—Howard T. Karsner, M.D. Page 45-A

Treatment of Cancers of the Anus and Rectum—George T. Pack, M.D... Page 48-A

The Relation of Pregnancy to Malignancy—Daniel G. Morton, M.D..... Page 57-A

The Treatment of Cancer of the Mouth with Irradiation—Charles L. Martin, M.D..... Page 59-A

Saturday, January 20, 1951

Morning Session

Recent Advances in Cancer Therapy—Danely P. Slaughter, M.D..... Page 64-A

The Treatment of Metastatic Cervical Lymph Nodes with Irradiation—Charles L. Martin, M.D..... Page 59-A

The Diagnosis and Treatment of Sarcomas of the Soft Tissues—George T. Pack, M.D.

Alleviation of Cancer Pain—Eldridge H. Campbell, Jr., M.D..... Page 71-A

THE JOURNAL
of the
KANSAS MEDICAL SOCIETY
Owned and Published by The Kansas Medical Society

Volume LII | Supplement to Issue for September, 1951 | No. 9

The Surgical Treatment of Cervical Cancer

Daniel G. Morton, M.D.

Los Angeles, California

In this dissertation on the surgical treatment of cervical cancer I hope to accomplish several things:

1. Dissuade all of you from having anything to do with it, except perhaps those few of you who are specially interested and equipped and have had a thorough training in pelvic surgery.

2. Persuade all of you that the treatment of cervical cancer in general is not something which should be undertaken by everyone. The job of those of us who are not especially prepared for this task should be to make accurate diagnoses as early as possible and if cancer is present to arrange for the patient's treatment by properly qualified persons as soon thereafter as feasible.

3. Assess for you the value of the various procedures now being carried out.

First of all, it is quite obvious that most patients with cervical cancer present themselves for treatment only after the growth has become quite extensive—certainly too extensive for effective surgical removal. In approximately 70 per cent of the cases the growth has extended well beyond the cervix at the time the patient is first seen. By and large these patients have an inoperable condition. In many other individuals, in whom the growth is relatively well confined to the cervix and thus suitable for operation from the point of view of anatomical extent, surgery is contraindicated by senility, obesity, cardiovascular or other disease. For these reasons, in the vast majority of cases of cervical cancer, irradiation remains the treatment of choice. In the minds of many authorities irradiation is the treatment of choice for all cases, and operation has no place whatsoever.

Within recent years there has been a renewal of interest in various operative procedures for cervical cancer, chiefly because of some of the drawbacks and complications of irradiation therapy. There has been a distressingly large number of late recurrences after irradiation treatment which has led to the feeling that actual removal of the cervix whenever possible would be an advantage. Cancer cannot recur in a cervix which is no longer present. Furthermore, irradiation has proven itself primarily ineffectual in certain cases, sometimes to destroy the local lesion and sometimes to affect metastases in the regional nodes. Since irradiation cannot be carried on indefinitely because of its destructive effects upon normal tissues, and because re-radiation is rarely successful, the only alternatives are surgical removal, or death from cancer.

First in importance among the operative procedures to be considered is the radical abdominal hysterectomy—or Wertheim operation. The object of this procedure is the removal of tubes, ovaries, the entire uterus, a wide portion of the parametrial connective tissue on each side, and several inches of the vaginal vault, in one bloc. The regional nodes on the lateral pelvic walls are also included. At one time this operation was accompanied by a 10 to 15 per cent surgical mortality. Today, with improved anesthesia, antibiotics, the free use of blood transfusion, and careful technical attention, the mortality should not exceed two per cent, and in some hands is less than one per cent.

The operation should be reserved for those cases in which the growth is confined to the cervix, and perhaps the immediately adjacent vaginal wall—in other words, Stage I cases (League of Nations Classification). The patient should be in good general condition, and not be obese; she should be relatively young. Elderly women with early cervical carcinomas should probably best be treated radiologically. Young women have a long life to look ahead to provided their cancers can be cured, and should be protected as much as possible from late recurrence. In my experience, only some 12 to 15 per cent of all patients presenting themselves for treatment are suitable for the Wertheim operation. One can expect to achieve a five-year survival rate of approximately 65 to 70 per cent. This figure will naturally be influenced by the proportion of very early cases included.

If we compare the results in surgically treated

cases (primary Wertheim operation) with those in radiologically treated cases of comparable extent, we find that the percentage of late recurrences (after five years) is much lower for the former than it is for the latter. Herein lies the chief advantage of the operation. The ability to remove the regional lymph nodes is probably largely responsible for this difference.

The chief complication of the Wertheim operation is injury to the urinary tract. Often the injury is not the result of direct trauma but of inevitable interference with the blood supply. Urinary fistulae will result in some 10 to 15 per cent of the cases. A few of these will be vesicovaginal fistulae; the majority will be ureterovaginal fistulae. The former may usually be repaired, while the latter often heal spontaneously, though occasionally with the loss of the kidney.

Here is a procedure then, which is suitable for a comparatively small number of early cases. It has distinct advantages over irradiation therapy, chiefly because of the fewer number of patients who develop late recurrences. It is, however, a comparatively formidable procedure. If mortality and complications are to be kept to the minimum, the operation should be performed only under ideal conditions and by those thoroughly competent to do so.

The Schauta operation is the radical vaginal operation by which the same local tissues are removed as by the Wertheim operation. It is impossible to remove the regional nodes through the vaginal approach, however. For this reason the Schauta operation has never been popular in this country. Its chief advantage over the Wertheim operation years ago was the lower primary mortality. Today the Schauta operation no longer enjoys this superiority. Recently Mitra, its chief advocate, has reported that he is now combining extraperitoneal lymphadenectomy of the regional nodes with the Schauta operation. No results will be available for several years.

The operation of pelvic lymphadenectomy deserves brief consideration. This procedure was popularized and championed by the late Dr. Frederick Taussig in 1930. His proposition was that in the early inoperable cases (Stage II, League of Nations), failure of irradiation frequently occurred, not because of the local cervical result which was often good, but because the regional nodes had already been invaded and irradiation failed to eradicate this spread. Upon the supposition that radium and/or roentgen irradiation was incapable of killing cancer when it has spread to the regional nodes, he attempted surgical removal of the susceptible nodes. His results seemed to show an improvement (about 15 per cent) when lymphadenectomy was carried out. We have tried out Taussig's idea and have not been convinced of its value as a therapeutic procedure. These operations afforded us an opportunity, however, of comparing the incidence of node involvement in a series of cases in which the patient had received no roentgen therapy preoperatively with another series of cases in which the patient had been irradiated by means of roentgen rays before operation. We found that the incidence in the former group was approximately three times that of the latter group, indicating that roentgen irradiation may indeed destroy cancer in regional nodes, at least in some instances.

With the diagnosis of carcinoma-in-situ being made more and more frequently, the problem of its proper treatment has come to the fore—and so far the choice has generally been surgical. The most authoritative opinions favor simple total hysterectomy with or without removal of the ovaries, depending upon the age of the patient. It has not been considered inadvisable to leave ovaries in young women since metastasis to the ovary is rare even with full-blown cancer. Simple cervical resection has also been employed for carcinoma-in-situ, especially in very young women desirous of having children. Dr. Norman Miller champions this idea; he has allowed a number of such patients to undertake pregnancy, and so far has had no occasion to regret his decision.

The most difficult problem in connection with carcinoma-in-situ is not so much treatment, for actually almost any form of treatment is likely to be highly successful, but the diagnosis. Before deciding upon treatment which is less than full irradiation or the radical operation, one should be very certain that the growth is "in situ." This can usually be decided only by multiple biopsies or by a "cone" biopsy. There is danger in the other direction also, that is operating upon inconclusive evidence. The diagnosis of carcinoma-in-situ is being made rather freely these days, and often unjustifiably in my opinion. I believe that one should have several confirmatory opinions before accepting such a diagnosis.

Finally we come to the question of secondary operations. More often than we would like, irradiation fails, cancer recurs or persists after full cancer therapy. What can be done about it? As stated previously, one cannot simply continue to expose the affected areas to irradiation because the tissues can tolerate only so much—beyond this necrosis sets in. Reradiation in smaller doses has never proven effective. We have surgical removal or death as our only alternatives. Usually surgical removal is impossible also, but occasionally there is a chance of removing the invaded tissues, particularly if we are willing to sacrifice adjacent organs. Brunschwig has championed this idea, as you know, and has shown

that it is possible to remove not only the whole uterus, adnexa, vagina, parametria and regional nodes, but also the bladder and rectum, and achieve good palliative results. Cures effected in this manner will be few and far between, but there will be some. Such operations, including less extensive modifications are associated with a very high primary mortality. They are expensive procedures, in terms of hospitalization, blood, antibiotics, complications and time. They are disappointing procedures, never to be undertaken lightly. Unquestionably, however, it is humane to undertake such procedures in occasional cases. We should be as certain as possible that there is good likelihood of improving the patient's condition, rather than the opposite. We must also realize that we are going to be wrong many times and we will achieve only the prolongation and aggravation of agony.

The surgical treatment of cervical cancer occupies several important niches. No operative procedure is applicable to all cases, but on the other hand I believe that it is wrong to close one's eyes to the possible advantages of surgery where it is specially indicated.

Therapy With Radioactive Isotopes*

John H. Lawrence, M.D.

Berkeley, California

The therapeutic usefulness of any given radioactive compound is dependent on three major factors: the affinities of the isotope for a specific tissue, the length of its radioactive half-life, and the depth to which its radiation penetrates tissue. The human body is so sensitive to radiation that as little as five r of x-rays delivered to the whole body will slightly inhibit red cell formation so that in delivering radiation to neoplastic tissue, the normal tissues must be protected.

The capacity of radiation to inhibit the growth of living cells is the basis for its therapeutic use. In addition to the three factors outlined above, mechanical factors such as the location of the neoplasm, its size, the type of tissue which is invaded, and the rapidity of cell growth are important. Low-Beer, for example, has developed a method of treating skin cancer by pipetting radioactive phosphorus onto small pieces of blotting paper and placing them over the site of the skin carcinoma. Since the beta rays from P-32 penetrate a maximum of only eight millimeters of tissue, the radiation is limited to a superficial area and does not penetrate the deeper tissues as is the case when the gamma rays of radium or x-ray are used. He has treated about 1,000 patients by this method. From 5,000 to 10,000 equivalent roentgens of radiation are usually delivered to the lesion. In the first 500 patients, approximately 95 per cent have five-year cures. This is selective irradiation by means of topical application (lantern slides).

Radioactive iodine is being used very widely in the study, and diagnosis and treatment of Grave's disease, and within the next five years may well replace surgery in most instances of hyperthyroidism. Because several hundred times as much iodine goes to the thyroid as to normal tissues, when the iodine is taken orally, one or two doses of Iodine-131 with potencies of from two to eight millicuries in each dose bring about a disappearance of the symptoms and signs of hyperthyroidism. After 10 years' experience, there has been no evidence that Iodine-131 induces cancer in any of these patients as far as I am aware. Certainly, it is the treatment of choice in patients in whom surgery is contraindicated or in patients over the childbearing age. Autoradiographs and other studies prove that the parathyroids do not take up radioactive iodine, and that the isotope is limited almost exclusively to the thyroid gland (lantern slide).

A test of thyroid function with radioactive iodine is now being widely used throughout the country, and many believe that it is an even more reliable test of thyroid function than protein bound iodine in the blood or basal metabolic rate. It is often helpful in deciding whether a true hyperthyroidism is present. The test consists of the determination of Iodine-131 uptake in the gland 48 to 72 hours after administration of a tracer dose. High, normal and low uptakes are seen in hyperthyroidism, euthyroidism and hypothyroidism respectively.

Radioactive iodine is occasionally helpful in diagnosing metastatic tumors. One patient under our observation who had no evidence of a thyroid tumor had a bony metastasis in the right hip. Although the pathologist did not suspect thyroid carcinoma, the ratio of uptake of radioactive iodine in the anaplastic tumor to the uptake in normal tissue was approximately five to one. Even though no primary carcinoma could be found, the diagnosis of

*This is a stenotypic transcription of the paper, presented with the aid of lantern slides.

thyroid carcinoma was thus established. The patient was subjected to a total thyroidectomy; the gland was sectioned; and a small carcinoma was found. At the end of two weeks a tracer dose of iodine was given. Marked uptake of iodine in the metastasis was found (lantern slide).

Treatment of thyroid cancer with radioactive iodine is less well established than treatment of hyperthyroidism. Large numbers of patients with metastatic thyroid cancer have, however, been treated since 1943. Although the end results are not yet available, sufficient evidence is present to indicate that persons who have metastatic thyroid cancer must certainly be studied with Iodine-131 and opportunity must be offered for therapy with this isotope if there is considerable concentration of the isotope. A small percentage of such patients will show uptake in the metastases when studied before ablation of the thyroid. A very large percentage of people who have thyroid carcinoma with metastases who do not take up iodine prior to thyroidectomy may develop uptake in the metastases afterwards. In therapy with Iodine-131, since one millicurie gives approximately one r whole body irradiation, excessive total body irradiation must be avoided. An instance of this danger is the case of a patient who was given over 500 millicuries of Iodine-131 over a period of six months. The red count and platelets dropped excessively before final recovery (lantern slide).

A patient with chronic myelogenous leukemia, on the other hand, is typical of many who have been carried for years with infrequent dosage of radioactive phosphorus, and in this case there is only slight localization of P-32 in bone marrow and in rapidly growing tissue. The red count remained high and the white cells were controlled satisfactorily. This patient developed a carcinoma in the fundus of the uterus in July, 1948, and a complete hysterectomy was performed. We are more concerned about the recurrence of carcinoma than about her leukemia; however, there has been no recurrence after a period of three years. This patient demonstrates the fact that the leukemic patient is certainly worth working with, and that some of them do exceedingly well.

Even childhood leukemia is not always hopeless. One of our patients, first seen at the age of 10, was treated with radioactive phosphorus from the beginning. Her white cells at that time numbered approximately 150,000. She was subsequently controlled with infrequent administration of P-32 for a period of 10 years (lantern slide).

Another patient, a woman in middle life, has lived 10 years with no treatment for her leukemia since the original treatment in 1941. She has apparently acquired an immunity to the disease and may go on for many years without treatment. In the series of over 300 patients with chronic leukemia treated during the past 15 years, the average duration of life after onset is nearly seven years in the lymphatic and four in the myelogenous group, and most of the life duration is comfortable (lantern slide).

Polycythemia vera presents a striking contrast to the leukemias in that it can be easily controlled by the use of radioactive phosphorus. People with high red cell counts, high red cell volumes, and enlarged spleens show typically a fall in the red cells and volume to normal levels when treated with radioactive phosphorus. In most cases, two doses of the isotope bring the count into satisfactory control, and in some patients it remains normal for 10 or more years without further treatment. A typical case is a woman of 36 treated when she had a red cell count of seven and a half million. Following two doses of five millicuries each, the patient has remained in satisfactory control for a period of about six years. Another patient with the typical symptoms and signs of polycythemia was treated with three doses of two, five and six millicuries respectively. There has been no recurrence of the disease (lantern slides).

About 30 per cent of patients with polycythemia vera will show such a result, needing no treatment for over five years. Others will have to be retreated. The average retreatment interval in a group of 200 patients is three years.

Therapy by means of radioactive isotopes is now being combined with hormonal treatment. In chronic myelogenous leukemia, patients with the longest period of duration are women; the patients with longest life duration in chronic lymphatic leukemia are men. There is considerable evidence that hormonal treatment is having a beneficial effect, but figures are not yet available to substantiate this impression. The practitioner who sees a patient with leukemia should not consider the case hopeless; this disease is not nearly as serious as lung carcinoma, stomach carcinoma and many other carcinomas. Many of these patients will outlive the doctors taking care of them, for a large number of them will live six, seven, eight or 10 years, or more. Give these patients the benefit of therapy and good follow-up care; see them at regular intervals so that if infections occur they have the benefit of antibiotic therapy; arrange for radiation therapy—either x-ray or radioactive phosphorus. The important thing is to treat these people with the assumption they are going to live a long time, and you will find

that many of them will live long and fairly comfortably.

In polycythemia vera, in the approximately 200 patients we have treated during a 14-year experience, the life expectancy is near normal. The average age of onset is about 54 and the average age of death about 68. These patients can be controlled very nicely with radioactive phosphorus. There is no evidence of late effects, such as the induction of leukemia or other complications due to the use of the isotope.

Passing now to the use of radioactive cobalt in therapy, we observe that this substitute for radium is used in the treatment of pelvic tumors. Cobalt, made radioactive in the atomic pile, has a half-life of about four years. It emits beta and gamma rays with about the same energies as radium. Low-Beer, Myers and others have used small cobalt beads, introduced with a Foley catheter, for the treatment of papillomatosis of the bladder. No large series of patients has yet been studied and followed so that at this time it is possible to say only that this is a substitute for radium and one can expect no better results than are available from radium, but it should be useful in therapy. It is also being used in the form of a "bomb" for teleradium therapy.

An effort was made in our laboratory to ascertain the usefulness of stilbamidine in the treatment of multiple myeloma. Reid, Calvin and Tolbert synthesized this compound, building radioactive carbon into its structure. It was given to animals and to patients with multiple myeloma; although the uptake of stilbamidine was greater in the myeloma cells than in normal cells, the ratio was not great so it had no application in radiation therapy.

Another attempt in this direction has been made by Pressman in New York. He immunized a rabbit to rat kidney. The antibodies from the rabbit serum were iodinated with radioactive iodine and then injected into another rat. The antibodies localized in the kidney as seen in autoradiographs. Such selective localization may lead to the development of an anti-cancer serum containing radioactive elements (lantern slide).

Fission particles travel only about one or two cell diameters in tissue. Based on this fact, the following experiments have been carried out by Tobias. A group of animals received some colloidal Uranium-235 intravenously. The colloid localized in the Kupffer cells of the liver. The animals were then shipped to Oak Ridge where they were placed in the atomic pile; fission was caused to take place in the atoms which were concentrated in the cells of the liver. A liver can thus be selectively damaged by the radiation. In a similar experiment, spleens were markedly damaged following their exposure to the pile. Although we do not intend to apply this method therapeutically, it is an interesting way to localize the energy of atomic fission within tissues.

Tobias also has been working with a very interesting new type of radiation which may eventually be applied to the surface of the body in the same way that x-rays and radium are applied. X-ray at the surface of the body has approximately twice the intensity as x-ray which has penetrated to a depth of 10 centimeters. High voltage deuterons from the 190-million volt cyclotron, on the contrary, give five times as great a depth dose at a depth of 15 centimeters as at the surface of tissue. Thus, for every roentgen delivered at the surface of the body, five roentgens are delivered to the depths. This energy can be directed with great accuracy: the pituitary body of a rat can be removed with a beam of this radiation. Carcinomas in animals have been irradiated experimentally by this method. It has interesting possibilities because it is possible to deliver much greater depth dosage to the tumor as compared to the skin dose (lantern slides).

Additional future applications of radioisotopes in therapy will depend upon our ability to find compounds containing them which will localize in the offending neoplastic tissue, and we may expect progress in this direction.

AMERICAN CANCER SOCIETY
RESEARCH
EDUCATION
SERVICE

Cancer and Allied Diseases in Children

Harold W. Dargeon, M. D.

New York, New York

It is a very great pleasure for me to have the opportunity of addressing you on one of the important problems in child health at the present time.

I would like to review briefly and rather broadly some of the aspects of this problem chiefly from the standpoints of diagnosis and etiology and show a few slides relating to the statistical incidence in the mortality figures in children.

As you know, we have witnessed in the last generation and certainly in the last decade a very dramatic and gratifying improvement in national child health. This has been due not alone to the use of the antibiotics and the sulfonamide compounds but to the broader application of many well known public health principles, pre-natal care of the mother, the delivery and post-natal care of the child. The former large group of killers of children is gradually being reduced and will be reduced further.

This has had the effect of giving us a larger population of individuals who will survive the hazards of fetal life, birth and post-natal life, and therefore assert intrinsic and some environmental problems which obviously they could not have if the diseases which previously took them off were still prevalent.

The deaths during the first year of life are still largely connected with diseases of fetal life, birth, and immediate post-natal life, such as congenital malformations, diarrhea of the newborn, various infections, etc.

After the first year, however, we begin to see the neoplastic group of diseases enter as an important factor in juvenile mortality. From the age of one to four in the particular group illustrated—1947—we find that neoplasms, and this includes histologically benign as well as malignant tumors and leukemias stood fourth among all the causes of death, and third among the diseases. Accidents are still the number one killer of American children after the first year of life.

In the five to nine year of age group, neoplasms stand first as the principal disease group. For the age 10 to 14 group, the same applies. Another point of importance from the standpoint of child health is that almost half of the deaths from these diseases in children occur during the first five years of life. A substantial portion of them, of course, are due to the leukemias, but another substantial portion of them could be salvaged if the measures that we know even now could be utilized in all cases.

The difficulty, of course is after the first year of life, at which time the child generally receives quite adequate care, he is examined periodically by his physician, or in many areas, in public health centers, receiving his inoculations. But after the first year, he may not be examined again until he goes to school. Within this age period, there are a number of curable malignant tumors and a number of curable benign tumors, but because of the fact that the child is not examined they are missed and they will continue to be missed until we have greater supervision of the run-about preschool age group.

Etiology. We of course don't know the cause of children's cancer any more than we know the cause of adult tumors, but we know something about some causative factors which are worth while recalling. The osteochondromas, and several other types of tumors, have a well known familial basis.

Neurofibromatosis has been known for many many years to have a strong familial tendency. This little girl (slide) has cafe au lait spots on the arm and a neurofibroma in the orbit.

Retinoblastoma, glioma of the retina, is known also in many cases to have a familial tendency, if not direct hereditary trait. Most all of the reported series of this tumor, which is a highly malignant one, have shown at least in a few instances parental disease as well as disease in the child. These (slide) are two little girls, the father of whom had retinoblastoma. They both have bilateral retinoblastoma.

Xeroderma pigmentosa has also been known for some time to have a trait associated with consanguinity.

Another possibility, presumably very rare, is transmission of the tumor, the maternal tumor, by direct extension into the placenta and then into the fetus. This child's mother (slide) had a nevus of the thigh known from early girlhood. When she was 18 it was noted that it had enlarged, her physician excised it and the biopsy showed malignant melanoma. She was married several years later. During her pregnancy her inguinal nodes enlarged, they were excised and malignant melanoma was present, and she went down hill very rapidly and had a Cesarean section before term. She expired several days later with very widespread malignant melanomatosis.

This patient's child at the age of seven months developed a weakness on the left side of its face and a discharge from the left ear. His physician, who was very much alert to the possibilities, had a biopsy taken immediately of some granulations in the external auditory canal which was diagnosed as malignant tissue, exact nature undetermined. Shortly after that he developed a nodule behind his ear, and biopsy of that showed malignant melanoma. He was sent to us, and he had a little melanomatous area behind the operative scar. He died four months later with melanoma in his lungs and an extensive melanoma in the liver. Whether or not this placental transmission could apply in numbers of cases, of course, we don't know.

It is an interesting possibility, however, knowing that influences act in adults to bring into clinical evidence certain diseases which have been present in the fetus, such as the ovarian dermoid cyst.

Another possibility for disease, of course, is development of cancer from irradiation. This can occur in the child as well as in the adult. This (slide) is a boy, a patient of Dr. George Pack, who was irradiated for an enlarged thymic gland as an infant. He was irradiated in a very good institution, and presumably the dose which was given, that is 600 roentgens, was not in the carcinogenic level. This boy had multiple basal cell carcinomas of the skin at the age of six.

Most of the tumors of children are congenital, certainly those seen in the first four or five years of life. They are therefore diseases of the fetus, and it is rather interesting that certain of them make themselves evident shortly after birth; others take a certain period to assert themselves. The very common one illustrated here (slide) is the hemangioma. They are seldom seen immediately at birth, most of them occurring in the first six months of life, as you know, and they are seldom seen after the second year of life. A very large portion of them regress spontaneously, and I believe from the standpoint of management this has to be taken into consideration. Certainly a child who has a hemangioma early in life which is cosmetically unpleasant, or functionally difficult, such as around the eye, around the lip, mouth, or the nares, the anus, or the vulva, should be treated quite promptly. If any one elects to observe other types, one really must observe them and observe them frequently. Just because a certain group of them regress spontaneously, one cannot determine at first examination—particularly in the early weeks of life—which category that particular tumor falls into.

Now the sites in which the tumors occur in children are rather different, as far as frequency goes, than the sites in which they occur in the adult. You are well aware of the common sites in the adult, but instead of the gastrointestinal tract, prostate, the pelvic organs, and breasts, we have other sites in which the tumors of frequent occurrence are found in the child.

These are the intracranial type, tumors of the orbit, tumors of the bone, tumors of the blood forming organs, tumors of the kidney, in which the outstanding one, of course, is the embryonal adenomyosarcoma or the Wilms' tumor, and those of the soft parts.

From the standpoint of clinical diagnosis, I think that we should consider that many of these areas are sites in which signs become present relatively soon. There is no such thing, obviously, as an early diagnosis in childhood cancer. Any tumor which has started in the fetus has had a chance to develop pre-natally for months, and unless it asserts itself very promptly after birth, as most of them don't, it has existed for months or maybe even years before symptoms present. Therefore, the earliest time we can make a clinical diagnosis is a moderately advanced or late diagnosis from the standpoint of the actual life of the tumor. When these orbital tumors do assert themselves they show quite evidently around the eye, as the illustration of the boy with the retinoblastoma demonstrated, with disturbance in the pupil and a defect in the vision. Intracranial lesions give rise usually to increased intracranial pressure and sensory and motor disturbances, and because a good many of them are situated in the posterior fossa, cerebellar disturbances frequently occur.

Tumors of the soft parts are quite difficult to differentiate but they generally follow a pattern. Swellings and lumps in the soft parts of a child are daily occurrences, but they usually go away. They go away unless there is something strange about them. When they do not go away they should be suspect, and they should be investigated.

Tumors of the marrow or the blood forming organs are generally indicated by anemias, peculiar anemias, or by other symptoms which we will discuss in another minute on the question of leukemia.

Tumors of the bones very frequently cause pain early. Children are not compaining individuals, as you know. They have to be prostrated, they have to be really suppressed even when they are sick in order to hold them down.

Tumors of the kidney. The Wilms' tumors, as you know, occur chiefly in the first few years of life when the mother is attending to the child very diligently. A great many mothers are discerning enough to palpate the baby's abdomen frequently

during bathing or changing diapers, even up to the age of two, but by that time they frequently escape close supervision.

I know of no exact way at the present time by observation alone or by palpation to make a differential diagnosis in every case of soft part subcutaneous swellings. Decisions regarding management are at times difficult. One doesn't like to recommend surgery around the face, around the neck or any other site where cosmetic possibilities have to be taken into consideration, but the cost of neglecting a soft part malignant tumor certainly has to be balanced against the cosmetic result.

Again, hemangiomas for example are histologically benign, and I think the general approach to the care of the child with a neoplasm, from the public health standpoint or the laymen's standpoint, should not be decided solely by whether it is histologically benign or malignant. We know very well that a very large number of people succumb from histologically benign tumors. But, to the layman, the word benign connotes safety. It doesn't mean what it means to us, and we should realize that when we discuss the subject with the layman.

Here (slide) is a child who has multiple histologically benign hemangiomas, showing subcutaneous nodules on the scalp and a nodule in the abdomen. That child succumbed of multiple hemorrhages from her benign tumor.

Lymphangiomas also are benign. They occur sometimes as small cysts which one sees on the tongue. They may be infiltrating in the soft parts around the face. A good many of them do occur in this area. One of the common types is the cystic hygroma which may be a single or multiloculated cyst. They may become infiltrating with diffuse lymphangiomatosis such as this little girl of five (slide) has had since birth. Here again we have a so-called benign tumor with a very serious prognosis in many instances.

Now, from the standpoint of diagnosis. How can we make an early diagnosis? I believe it is necessary in children, as well as in adults, to weigh not only the frequent possibilities in the diagnosis and the differential diagnosis but also the necessity of emergency intervention if anything else except the more frequent possibility presents.

Note the difficulties of making a diagnosis of leukemia illustrated here. There may be anemias; we may have weakness, we may have swellings—these infiltrations in various sites. Lymphadenopathy from acute infections is a very common finding in general pediatric practice. Infiltrations in the viscera or in the tonsil and adenoid area may be due to leukemic infiltrations or to other tumors.

Fevers of unkown origin should always be suspect, not only of some of the more esoteric infectious diseases but also of tumor; and leukemia may at times run a course with a pyrexia and even sometimes with a normal peripheral blood and bone marrow. We have observed one child in whom everyone suspected the diagnosis of leukemia but a positive diagnosis could not be made until after he had been running a fever for over four months.

Myalgias are very commonly due to orthopedic problems and, of course, rheumatic disease which is quite prevalent in children. But about 10 to 15 per cent of all leukemias start with pains around the bones, pains in the legs, pains in the feet. Bleeding, of course, is more often a symptom of late leukemia than an early one, but we have often seen leukemias in which the diagnosis is not made by peripheral blood until many, many months after an initial hemorrhage was seen in the skin.

Another illustration of the problems in differential diagnosis are those in the intracranial group. A great many of these tumors, probably 50 to 60 per cent of those in children, occur in the posterior fossa and they give rise to cerebellar symptoms. There is another group which occurs in the hypophyseal area and then others scattering in the cortical areas and in the structures surrounding the brain. Naturally these can give rise to multiple groups of symptoms. They can be gastrointestinal. They can be sensory. They can be motor. They can be psychic. These children are referred to orthopedic men. They are referred for eye examinations. They are referred to psychologists; and all the time they may have an intracranial tumor.

Dr. Bucy is authority for the statement that a good portion, at least one third, of all the intra-cranial tumors in children are curable if treated early.

The neuroblastoma. This is an embryonic type of tumor which arises from the sympathetic neuroblast and it is generally, unfortunately, diagnosed only after metastases have occurred.

If we consider the areas of the body in which sympathetic tissue is distributed, we can arrive at the problems in diagnosing, or the possibilities of diagnosis in this tumor. There are cervical, thoracic, lumbar and sacral sympathetics. There are cranial nerve ganglia. There is the cardiac ganglia. There are the celiac plexus, the aortic bodies, the hypogastric plexi and also the adrenal medulla. Now a tumor distributed anywhere along here may cause not only local symptoms but possibly systemic problems.

One of the common primary sites of the neuroblastoma is in the abdominal areas and in the adrenal medula. They may be suspected if an abdominal mass is felt and calcification is visible by roentgeno-

gram. Here is illustrated (slide) a very, very large calcified area in a neuroblastoma. Not very many of the other abdominal tumors calcify. There are exceptions, however, which we will see. Neuroblastoma is a presumptive diagnosis if a calcified area is found in an abdominal mass, particularly a small abdominal mass.

Here (slide) is a neuroblastoma arising in the cervical sympathetic without any other signs, and the next case is one of a neuroblastoma arising apparently from the skin of a child. It was just a small nodule, ecchymotic, considered, as one would, to be due to a contusion, but it did not go away. Here I think is a clinical hint aiding in the diagnosis of children's tumors. The disease, or the disturbance, doesn't follow the general expected pattern in childhood. There is something strange about it; if a contusion doesn't go away, if a fever doesn't go down, if the pains don't disappear when the usual therapy is administered for rheumatic infection or orthopedic corrections, look further, and frequently the diagnosis of tumor can be established.

The next two cases (slides) are cutaneous varieties of neuroblastoma. The first shows multiple nodules, the second only a few. The latter baby was treated some 14 years ago, and has now survived.

This (slide) is a cervical or supraclavicular node enlargement following, or associated with, a hemangioma which had been treated. This child had metastases into the supraclavicular nodes from an intrathoracic primary. Biopsy of this mass showed neuroblastoma, and that child was treated by irradiation, x-ray, and that child has survived.

Neuroblastoma is among the very highly malignant tumors in childhood, but here again, as Dr. Lawrence pointed out, don't throw up your hands even though the prognosis is very doubtful because there are many instances, not only ours, but others, of patients with neuroblastomas who have survived a good length of time, even those with metastases such as we showed you. Here (slide) is a boy who has survived approximately 12 years now, another child who has lived five and a half; another one five and a half; another one four and a half.

The Wilms' tumor, the embryoma of the kidney, is also another embryonal tumor, and is seen usually between the second month and the fourth year of life. It may occur bilaterally, and the parent who feels a tumor mass in the abdomen is often the first person who suspects trouble.

Any abdominal mass which shows on urogram displacement of the kidney might be suspect, although one must consider lymphomas, neuroblastomas, and teratomas at times. But the important thing from the child's standpoint is that it requires surgery, and requires surgery very promptly with a minimum of delay. We don't believe preliminary irradiation should be practiced—first, because of the delay required for an adequate dose of irradiation; second, because of the fact that many of these Wilms' tumors don't diminish by irradiation; and third, because irradiation sometimes doesn't produce the desired effect in killing all the cancer cells.

This (slide) happens to be a bilateral Wilms' tumor which of course is a hopeless situation. Here is a Wilms' tumor in which a large area of calcium was laid down in the body of the growth. I just bring that in to illustrate the necessity of caution in making diagnosis roentgenographically, clinically, or even pathologically. The pathologists are well acquainted with the problems facing them in the differential diagnosis of some of the lymphomas, some of the embryonal myosarcomas and some of the neuroblastomas. The radiologist and the roentgenologist are also similarly aware of the difficulties of diagnosing not only one tumor from another in the study of a bone, but differentiating non-neoplastic disease from neoplastic disease.

A diagnosis of neoplastic disease in a child as well as in an adult implies a good deal of radical and aggressive treatment. Children who have to live their whole lives are in a somewhat different category than an adult of 25, 55, or 65 who has had his life. A child who is handicapped by the results of therapy, even where it is justified, has great social and psychological adjustments to make. Therefore, before a procedure is undertaken, and it certainly should be undertaken if it is required, all factors should be considered. The history, the physical examination, the roentgenograms, and the pathologist's diagnosis must be evaluated carefully before the management is decided.

It is not correct to throw the weight of the diagnosis entirely on the shoulders of the pathologist or the roentgenologist. All physicians with the case are involved.

Here (slide) is a very common disturbance in children. Subperiosteal hemorrhages of the newborn occur in numbers in many maternity hospitals. This child was originally suspected to have a Ewing's tumor which it did not have.

The next roentgenogram (slide) shows a periosteal elevation and slight thickening of the cortex in a child of seven, also sent to us with a diagnosis of Ewing's tumor, which it did not have. It was a so-called march fracture, and the child made an uneventful recovery.

We are, therefore, faced with a problem in childhood perhaps a little different than it is in the adult. The child cannot complain, or doesn't complain. He is entirely dependent upon his parent

for care and for frequent examination; and the parent is entirely dependent upon the physician for judgment as to procedure. It is not correct for any one of the team involved to have the other accept the responsibility. Everybody must work together, and certainly the family physician who sees the child first is not only an essential member of the team, but probably the quarterback and the coach who really calls the signals that are going to determine the child's future.

Surgical Treatment of Advanced Cancer

E. D. Sugarbaker, M.D.

Jefferson City, Missouri

During the past 10 years, a tremendous amount of emphasis towards radical surgery in the enormous group of diseases that we have chosen to call cancer has taken place. There has been a great deal of discussion in all branches of medical literature, particularly the surgical, as to the justification for many of these procedures, and I believe that a great deal of that discussion and a great deal of that questioning has been justified. I shall try today to set forth as clearly as I am able my ideas on what is radical cancer surgery, and what is advanced cancer, and where the two should meet.

In concept, surgery is an extremely simple method of treatment. Indeed, it is the simplest of all methods that have been chosen, and it depends entirely for its success on the ability of the operator to completely remove the tumor. One might even say that surgery is a crude method of treatment, far less refined than that employed by our radiologic colleagues, whose implements act in a manner far too complex to be as yet completely understood. Surgery utilizes the age old principle of separating the evil from the good.

One might pause here for a moment to define briefly when, in general, the two commonly accepted methods of treatment mentioned above are more applicable. Surgery is generally employed when: (1) the limits of the disease seem well demarcated; (2) the anatomy lends itself well to wide removal of both the primary and the draining node areas, and (3) the tumor is not one of reasonable radio-sensitivity. Contrariwise, irradiation is generally used when: (1) the limits of the disease are difficult to determine; (2) the anatomy does not lend itself well to wide removal of both the primary and the affected or potentially affected draining lymph node areas; (3) one is dealing with a tumor of reasonable sensitivity.

We have heard some reference in this regard already this afternoon as it applies to the radical removal of carcinoma of the cervix, in which instance one is limited in an attempt at any wide removal by the bony wall of the pelvis. It is quite reasonable in such a circumstance to restrict one's surgical efforts to those cases in which the disease is well confined to the cervix.

Surgery has several drawbacks which must be considered. First, it may leave behind an anatomical defect. I should like to say here, however, that the anatomical defects following the employment of surgical methods are not difficult to correct since the tissues do not present the problems in healing which remain following heavy irradiation. Following the surgical extirpation of tissue of great cosmetic or functional significance, the adjacent tissues remain in an undamaged condition, and lend themselves easily to subsequent reconstruction.

A great deal was once expected of irradiation therapy, and many of these hopes have been abundantly realized. There was a day when surgeons were able to accomplish much less with many cancers than is possible today because of the dangers of shock and infection and the difficulties of anesthesia.

Intrepid individuals in the field of radiology, willing to suffer the hardships of the pioneer in any field, brilliantly attempted to sound the potential accomplishments of irradiation methods in some of these tumors which had responded so poorly to the surgical attempts of that day. That a great deal of over-enthusiasm prevailed at that time was only to be expected and in hind sight deserves commendation, when one considers the enormous problems involved. Though irradiation has not fulfilled these high expectations, in many instances it has more clearly defined the responsibility of the surgeon. Not only have its methods all too often failed to cure, but we are now beginning to recognize some of the unfortunate life-long effects which they are producing. I was very glad this afternoon, in an earlier paper, to hear of the choice of surgery, especially in young individuals having the less advanced forms of cervical cancer. These individuals only a few years ago would have been exposed to x-ray therapy with the consequential sacrifice of their ovarian function and considerable damage to im-

portant normal structures such as the intestinal tract and bladder.

During this same period of critical assessment of irradiation therapy, surgery has made many important advances, with the result that the majority of its former serious complications have largely been eliminated. I do not feel that I need to re-enumerate these since they are well appreciated by all. Suffice it to say, however, that it is not at all strange to witness a general resurgence of surgical enthusiasm toward the treatment of a great many of the tumors, which were shrouded in pessimism a few years back. The result has quite properly been that new fields are being explored and will continue to be re-explored and re-evaluated with the continued progress of the future. Its most serious limitation, which unfortunately also applies to currently employed irradiation methods, is that it is strictly local in its application and we are, unfortunately, dealing with a disease which always inherently tends to become generalized, or indeed, may already be so, at the time treatment is instituted.

Cancer spreads by direct extension or local invasion, and by involvement of lymphatic and blood capillaries. It is this tendency to invade which leads to lymphatic and blood capillary permeation, and to the involvement of adjacent organs. When lymphatic embolization takes place, arrest of the emboli commonly occurs in the next adjacent group of lymph nodes. Blood vascular emboli are usually halted in the capillary bed of organs receiving quantities of venous blood such as the liver and lungs. Apparently some may pass the lungs and enter the arterial system, whence the possibilities for metastases become much more numerous. The surgeon must assume the responsibility for local invasion and accessible lymphatic spread, for these are usually within his sphere of influence. He cannot be held responsible for dissemination via the hematogenous route since as yet he possesses no means of controlling such tumor spread. Rarely may hematogenous embolization be recoverable and then only when it is solitary and in a removable structure.

Factors Influencing Surgical Removal

There are several factors which should be considered since they strongly influence the extirpation of many cancers. Foremost to be considered is the surgical tolerance of the patient. Although cancer does occur in children, unfortunately, by and large the incidence of cancer rises with each succeeding decade of life as insurance statistics so clearly show. Increasing knowledge of how to favorably influence the surgical tolerance of the patient has been the most important element in increasing the scope of surgical treatment among cancer patients. Though we are learning to surmount the complicating difficulties concerned with coincident diseases of the cardiovascular renal system and of nutrition more and more each day, they still do exist and still will frequently require very careful consideration. The management of shock and infection is now so well known as to require no elaboration.

The personal factor of increasing technical experience, in some of the peculiar procedures carried out for cancer alone, might also be mentioned at this time. There are few instances in which the mental and technical agility of the surgeon so diminishes the wear and tear on the operative patient as in extensive resections done on elderly individuals.

The second important factor relates to the anatomical setting of the tumor. Tumors arising adjacent to and invading vital structures such as the heart, aorta, common carotid artery, etc., by their location alone frustrate any attempts at surgical removal, even though they may not as yet have metastasized. Tumors arising in areas that are closely confined will present technical difficulties in exposure. One of the commonest frustrations to accurate surgical removal is troublesome bleeding which obscures the surgical field.

The complete removal of a cancer requires a degree of accuracy beyond that required for the removal of a gall bladder or for repair of structural defects, and the exposure demanded is in direct proportion. It has been my own experience that whenever malignant tissue has been cut across, even though it was recognized immediately and adequate steps were taken to widen the removal, the patient has not been cured. The oral cavity, where the smallness of the working space makes exposure difficult, is a commonly encountered example. Under such circumstances, we routinely do a temporary tourniquet ligation of both external carotid arteries. This renders a completely dry operative field. Those of you who have done any amount of head and neck cancer work know that as soon as one loses his bearing in this region, he is very apt to lose control of the entire situation. We carry out a similar procedure in the pelvis, preliminary to any extensive resection. Both internal iliac arteries are preliminarily ligated, usually using a tourniquet-like ligature, which may subsequently be removed in order that healing may not be interfered with. In abdominal operations of this caliber the necessity for anesthesia which affords complete relaxation and the benefit from generous incisions should be thoroughly appreciated by every surgeon.

The third factor, and that whose influence is still by far the greatest, is the extent of the disease. This is not subject to the surgeon's influence, but is something which must be accepted as it exists. Since

the terms "early," "late," and "advanced" are meaningless as applied to a given cancer setting, we should like to avoid any ambiguity by using the phrase "extent of the disease" and defining it as an expression of time and the biologic activity of the cancer:

Extent of disease = Time × biologic activity.

From such a simple formula it becomes apparent that a tumor of high biologic activity, even though it may be diagnosed relatively early, may easily be beyond the control of the surgeon. It may also be appreciated that tumors frequently termed "advanced" may simply represent tumors of low biologic activity, which perhaps have expended a great deal of their energy in local growth over a rather long period of time. These may still be easily amenable to surgical removal.

We may combine all of the factors involved into one very simple equation:

$$\frac{\text{time} \times \text{biologic activity}}{\text{treatment}} = \text{prognostic index.}$$

Where the general condition of the patient will permit and where the setting of the tumor lends itself to wide and extensive removal, the treatment factor will be large, and the prognosis will be influenced favorably. Where the biologic activity is high or the time factor is long, the prognosis will be altered unfavorably. Considering such a simple equation, it then becomes readily apparent why a cancer of the pancreas or a cancer of the esophagus, both tumors of high biologic activity occurring in locations where they are not diagnosable early and in which the limits of surgical removal are narrow, offer an extremely poor, usually hopeless prognosis.

Biologic Activity

A brief discussion of what is meant by biologic activity might here be in order. First, let it be said that if the implications of this term were thoroughly understood, the problem of cancer treatment might largely be solved. There are some aspects of it, however, which are quite tangible, and when considered in relationship to one another contribute considerably to a better understanding of the clinical problem involved. We must first distinguish between those tangibles which should properly be called influencing factors and those which are simply expressions of the factors involved.

Age and sex are well known to influence the activity of many tumors. Pregnancy and lactation exert an extremely unfavorable influence on mammary carcinoma. The benign course of melanoma preceding puberty, and its extremely malignant course following that period of hormonal turmoil, are known facts. The site of the tumor, its histologic type and grade are well known influences. The dissimilarity of behavior, of epidermoid carcinomas of the hard palate and of the tongue, for example, are well known. The differences in behavior peculiar to sarcoma and carcinomas have long been known and the increasing tendency for metastases of the higher grades of tumors is also well known. Many of these factors might be mentioned, but the above will serve as examples. Suffice it to say that such factors peculiar to any given tumor should be thoroughly understood and considered before definite treatment is undertaken.

Those aspects of biologic activity which are expressions of the above mentioned influences must be considered in their relation to the probable time factors involved. The size of the primary, the relationship of appearance of node metastasis to the state of the primary, and the number of nodes involved are expressions which, when considered relative to the time factor involved, provide vital information.

Figure 1-A. Patient presenting a thyroid adenoma with a tumor of 20 years duration involving left upper extremity. This proved to be a metastasizing struma (solitary).

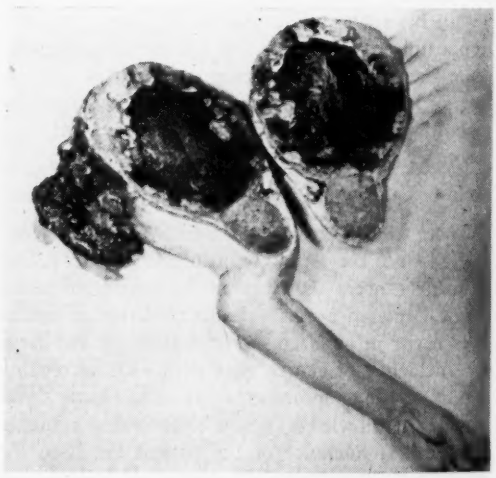

Figure 1-B. Interscapulo-thoracic amputation specimen. Marked cystic degeneration with total absence of the humerus.

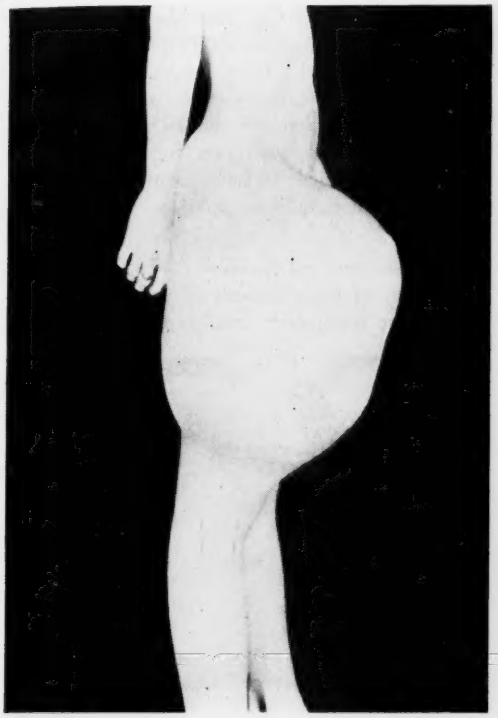

Figure 2-A. Enormous chordroma of the femur. The specimen removed by disarticulation of the innominate bone weighed more than half of the preoperative weight of the patient.

Figure 2-B. Patient alive and well eight years after operation.

The aims of surgical treatment are first, and foremost, cure; and secondly, to obtain palliation. The meaning of cure is clearly apparent. The term "palliation" has come to be too loosely used and is frequently belied by the results obtained or by the amount of physical hardship imposed on the patient in an attempt to obtain it. Dorland states that "palliation" is "that which affords relief but does not cure, or to reduce the severity of." Webster's definition uses the phrase "to reduce in violence." It does

Figure 3-A. Enormous chondromasarcoma involving entire right innominate bone. Hindquarter amputation involved removal of entire right ala of sacrum opposite pubis and portion of prostate.

Figure 3-B. Patient living and well four and one-half years after operation. (Died of a stroke shortly after photograph was taken).

not appear to us to be reasonable to impose extensive operations on a patient in whom the benefits to be obtained are at the outset highly problematical and which, in the final analysis, amount to a prolongation of life measurable in days, weeks, or even a few months of continued misery. There can be no question of the benefit to be obtained from the relief of obstructive lesions of the alimentary tract, for example, since these are often the source of considerable discomfort to the patient. However, when all chance for cure is known to be passed, it would seem reasonable to confine one's efforts to procedures of less than extreme major proportions. Experience teaches and it is well to bear in mind that under circumstances thought to be much more favorable than those already assessed as being hopeless, a reverse form of palliation is occasionally obtained.

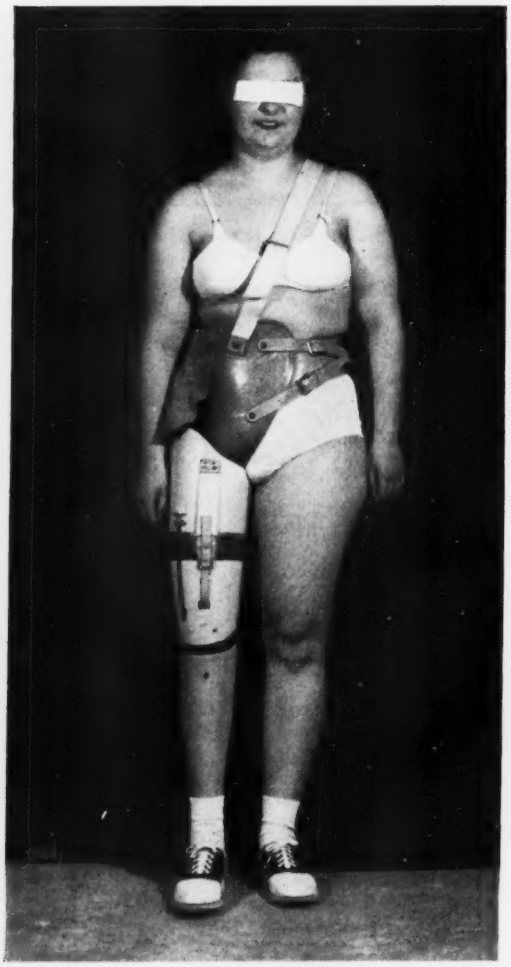

Figure 4. Patient previously subjected to disarticulation of the innominate bone wearing a prosthesis.

With this as a rather lengthly introduction, I should like to present three groups of cases, with the results obtained. They consist of patients in whom the extent of the disease had reached such proportions as to demand unusually extensive surgical procedures if any hope for its eradication might be entertained. In each instance cure was the goal, but palliation was often a gratifying by-product.

Forequarter and Hindquarter Amputations

The first of these consists of extended amputations of the forequarter and hindquarter type. Of

Figure 5-A. Large ulcerating submaxillary node invading mandible (primary-buccal mucosa).

Figure 5-B. Jaw resection and neck dissection combined. Function excellent. Living and well nine years post-operatively.

Figure 6. En bloc specimen consisting of entire lower lip, hemimandible and contents of one side of the neck.

the hindquarter amputations nothing less than a disarticulation of the innominate bone was accomplished, and in several a portion of the sacrum and opposite innominate bone was also removed. Five of the 13 patients are living and well for four or more years. One is presently living with a pulmonary metastasis, which we intend to remove.

The histologic diagnoses among these long term survivors are, I believe, highly significant. One presented an extensive condroma of the femur and soft tissue of the buttocks, the entire specimen weighing 55 pounds. The second presented an extensive chondrosarcoma of the entire right innominate bone. Another presented a fibrosarcoma of the soft tissues about the axilla; the fourth an extensive epidermoid carcinoma of the entire upper arm, shoulder, and anterior chest wall region; and the fifth a metastasizing thyroid struma involving the humerus and shoulder region. By and large, these represent tumors of low to medium biologic activity, which is at once the explanation for their survival and the reason why the procedures carried out were considered worthwhile.

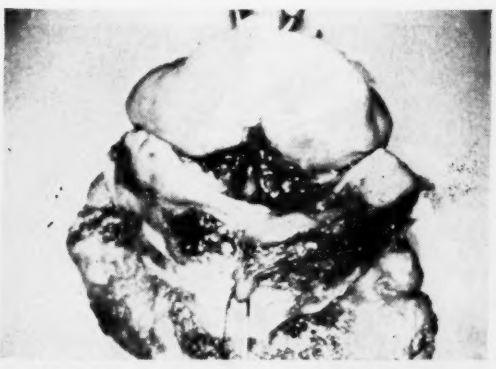

Figure 7. Carcinoma of the floor of the mouth. En bloc specimen consisting of the anterior half of the tongue, the posterior sagittal half of the anterior mandible (the anterior sagittal half remained as an intact bridge) and the contents of both sides of neck.

Resection-Dissections About the Head and Neck

The second group were treated to extended resection-dissection operations about the head and neck structures. Such removals usually involve the primary tumor in continuity with its draining node area. Included in addition to the neck dissection was a removal of the parotid, the mandible, tongue, palate, maxilla or mandible, etc. In all there were 78 procedures. Twenty-five patients had primary disease and node disease simultaneously present and removed in continuity with whatever additional structures were indicated. There were two postoperative deaths, but seven of the patients are still living and well (28 per cent). Twenty of these patients had carcinomas of the epidermoid variety, and five are living and well.

Of those patients in whom the disease at the time they were first seen was confined to the nodes or had extended from the nodes to involve some adjacent structure, there were 21. In these patients

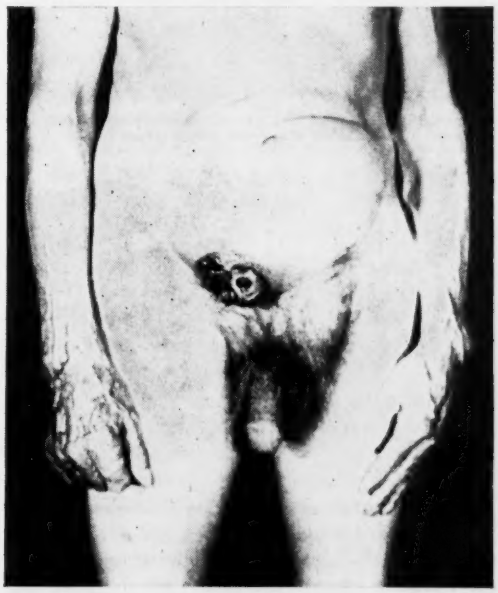

Figure 8. Bulky carcinoma of the colon fungating through the abdominal wall. Easily resected with wide removal of abdominal wall.

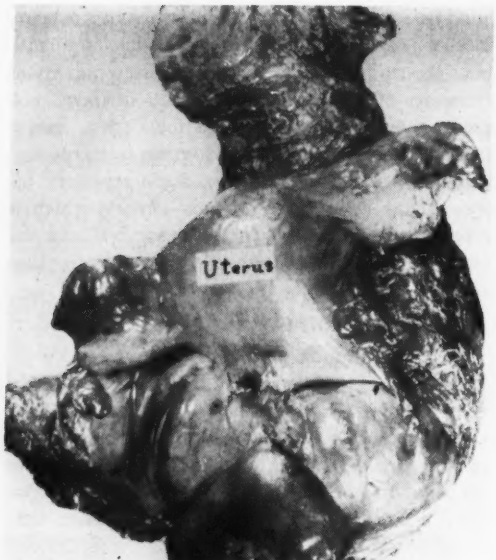

Figure 9-A. Carcinoma of rectosigmoid resected with adherent uterus and small bowel.

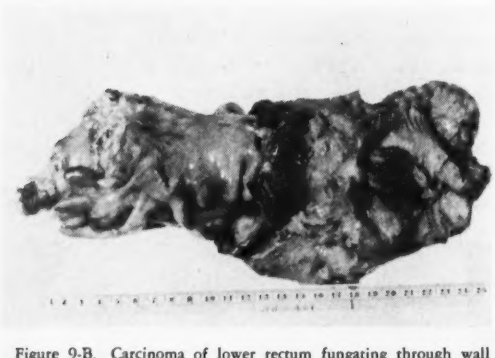

Figure 9-B. Carcinoma of lower rectum fungating through wall of vagina. Bowel resected with entire female genital tract.

Figure 9-C. Rectum resected with entire retro-urethral portion of prostate.

the primary had been successfully treated prior to the time the patient was seen with the node disease. There were three post-operative deaths, but 11 of the patients are living and well for long periods of time (52 per cent). Of the epidermoid carcinomas requiring such extensive removals, an excellent prognosis may be anticipated from those of low histologic grade in which the nodes are not coincidentally present with the primary, and in whom the interval between treatment of the primary and the first evidence of node mestatasis is 12 or more months.

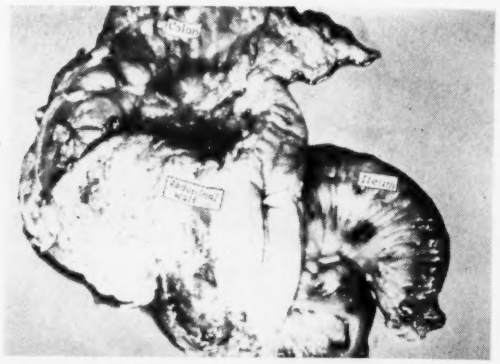

Figure 9-D. Carcinoma of cecum extensively invading abdominal wall anteriorly and laterally.

Of the resections done, in which the nodes proved to be negative for evidence of metastatic disease, there were 32 in number, of which 22 or 70 per cent are living and well.

Extended Resections of the Colon and Rectum

The third group consists of extended resections of the colon and rectum and includes only those patients whose tumors had extended to involve one or more adjacent organs. In all there were 65 patients. In approximately two-thirds a single additional structure was removed, and in the remaining one-third, more than one structure or organ was removed. Thirty-two of the entire group are living and well for long periods of time. Eighteen of these have now survived more than five years. In review-

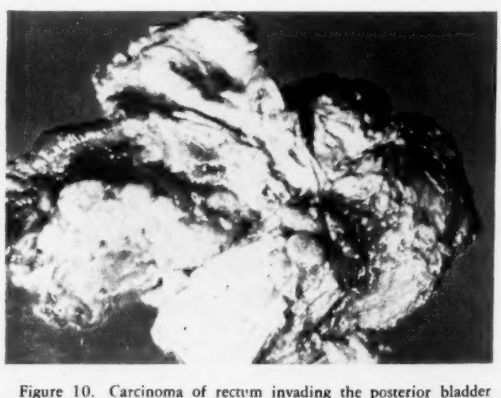

Figure 10. Carcinoma of rectum invading the posterior bladder wall. Bowel and bladder resected; sigmoid and anus anastomosed; ureters implanted in the sigmoid; unpleasant wet colostomy avoided.

ing the ominous pathologic factors in these tumors, the higher incidence of lymphatic, vascular and perineural involvement was noted. *In 40 per cent, the sole ominous pathologic feature was the local extension.* In other words, these represented a group of cancers of the large bowel which appeared to content themselves entirely with local growth with no inclination to metastasize, and it is this group which justifies any amount of surgical effort to obtain their complete removal.

In concluding, I would like to say that the term radical surgery has come to mean very little. It is relative only to the times during which it is used. Procedures which we formerly thought to be quite radical, which were done only occasionally, with considerable trepidation have now become commonplace. Many of the procedures shown here today were considered to be most unusual and highly radical when they were first accomplished, and are now being generally done in a rather matter-of-fact sort of way. It seems safe to predict that as long as improvements in management of technic continue, this trend will keep pace with it. The surgeon must always study his patient with extreme care and be unstinting in his efforts to provide all that his art affords.

Conclusion

1. The present day position of surgery in the treatment of cancer is briefly reviewed.
2. The factors influencing the complete extirpation of cancer are discussed.
3. The particular influence of biologic activity of tumors and what it implies is stressed.
4. The relationship of surgical treatment to the extent of the disease and prognosis is presented in the equation:

$$\frac{\text{Time} \times \text{Biologic activity}}{\text{Treatment}} = \text{Prognostic index.}$$

5. Several types of cases which required extended surgical procedures are presented as exemplifying this relationship.

Congenital Defects and Associated Neoplastic Disorders in Children

Harold W. Dargeon, M. D.

New York, New York

During the last decade there has been a very great stimulus to the studies of diseases of the fetus. This has been perhaps accentuated by the well known findings of the malformations which occur in the fetus during pregnancy of women who have suffered from German measles. There has also been experimental work done, particularly by Warkany and his group, on the nutritional aspects of determinants causing congenital malformations. So we are at present deep in the study of the possible causative factors, environmental as well as inherent and intrinsic in the individual, which under certain favorable conditions will terminate in what are called anatomic malformations.

We know that in the neoplastic field a great proportion, certainly most all of the tumors which occur in children before the fifth year, are of congenital origin. The cause behind this we are quite unacquainted with. In the environmental field, we are aware that in the adult various environments will produce in certain individuals the disorder we call cancer.

But whether environmental factors will produce this disease in the fetus, we still have to determine. It is of speculative interest to consider the cause or causes of the simultaneous appearance of an anatomic defect and a tumor in the same child. It would be highly improper in our present state of knowledge to postulate a relationship, but nevertheless, regardless of the ultimate conclusions about this relationship, the coincidence may be of clinical value to the physician in charge of the child.

I would like to show you some of these situations which we have encountered at Memorial Hospital and elsewhere. Examples are to be found, as usual, in much of the old literature, but I don't believe they have been stressed quite enough, and I would simply like to illustrate a few of these incidents.

Here (slide) is a child with a supernumerary digit and a Wilms' tumor. The child was sent into the hospital for removal of the supernumerary digit, which was done. It was a hospital where every child is given a complete examination, and several days after the surgery was performed the pediatrician examined the child and found an abdominal mass which, on operation, was found to be in the renal area and on pathological examination was proven to be a Wilms' tumor. This child subse-

quently died from metastases of his tumor. A necropsy was performed, and in the esophageal wall there was a bronchiogenic cyst also.

This (slide) is a child also with a Wilms' tumor with abdominal spread. He was receiving irradiation over these fields at this time. He also has congenital cataracts.

This (slide) is a cystic hygroma, a tumor of lymphangiomatous nature, and a congenital malformation of this left leg. I think the difference in the circumference of the left leg, as well as the length, is evident. This is a radiograph of the child showing the large cystic mass. A point in management we mentioned yesterday might be repeated here, namely the spontaneous regression of certain of these tumors, particularly hemangiomas but occasionally also in this type of tumor. This is not an easy tumor, in many instances, to remove surgically. It is not responsive to treatment by irradiation and radium; sclerosing solutions sometimes have been used with success, but surgery seems to present the most favorable type of therapy. However, the tumor frequently involves many important structures in the neck and may have extensions down into the thorax so that a surgical procedure may be quite formidable. It has been our policy to postpone major surgery in children, if not urgently required, until the age at which the child could withstand a major procedure. This is generally better tolerated—after the immediate neonatal period—after the age of two. In waiting for the period to elapse, however, we found the hygroma regressed spontaneously in this case. We have had two such experiences with hygromas although they are not reported very often in the literature. Here (slide) is the child two years later. You can see that her left leg is still a little bit shorter than the right, but actually it is growing and it may compensate eventually.

This (slide) is a radiograph of the left hand of a child five years of age. I think that you can see in the first metacarpal bone that the normal concavity of the shaft is present and also that the soft parts shadow is quite flat. The thenar eminence was lacking; she had a congenital absence of the muscles of the left thenar group. On the right hand, I think you can see the difference in the size of that metacarpal compared with the one on the left, a broadening of the shaft, and this bulge of the soft parts. On this hand she had a tumor which was removed and was found to be an embryonal rhabdomyosarcoma, and she succumbed about four months later from pulmonary metastases. She had had the tumor on her hand for five years and it had been seen by hundreds of people.

This (slide) is a boy with a lymphosarcoma of the parotid who also has a patent ductus arteriosis. This picture was taken three years after irradiation to that tumor. The child has survived four years. For those who take a dim view of the possibilities of any child with a malignant tumor, I think it is worthwhile to remember that even lymphosarcoma, one of the most highly malignant tumors, may be amenable to therapy.

Here (slide) is a child with several defects, malformation of the nose and a hemangioma of the lip. The child, up to the age of nine months, had been progressing satisfactorily, but then began to show muscle weakness. He didn't want to stand, then he didn't want to sit, and later he failed to even crawl around in his bed. Examination showed separation of the sutures, Macewen's sign and bilateral choked discs. This roentgenogram shows dilated ventricles, and it was assumed that he had a posterior fossa tumor, probably a hemangioma. At operation he was found to have an astrocytoma of the cerebellum.

The next case is that of a boy nine years of age who has multiple cafe au lait spots, congenital malformations of the vertebra, gynecomastia and a lymphangioma of the neck. He has several osseous defects, including a cervical rib, fusion of several vertebra and a mass in the superior thoracic area on the left which has not been removed as yet. He also has these osteolytic areas in the bones.

Here (slide) is a child with one cafe au lait spot on the back, another on the abdomen, a hemangioma on the foot and a lower abdominal mass. On the ear he had a verrucous like growth. The abdominal mass was excised quite completely and it was found to be a rhabdomyosarcoma.

In summary, I would say that whether or not anatomic congenital malformations and neoplasms in the same individual have a causal relationship is unknown. However, an opportunity exists here, I believe, for every physician who treats children to contribute to a long time study of congenitally malformed individuals, not only during their childhood but also to determine later on during adult life what, if any, neoplastic tendencies the individuals who have such congenital anatomic malformations may present.

Carcinoma of the Breast

Everett D. Sugarbaker, M.D.

Jefferson City, Missouri

This morning we have a subject which, I trust, will remain interesting to you. It certainly is an extremely important subject, one about which we should know a great deal more than we appear to know. I believe that among the mistreated cancers we see, cancer of the breast occupies a prominent position. It would appear that it is mistreated as often as any other tumor, in spite of all the information we now have available regarding it.

Carcinoma of the breast is a disease of the breast parenchyma, and occupies a position of intermediate malignancy in the gamut of tumors insofar as life expectancy and five-year survival are concerned. It makes up approximately one-fourth to one-fifth of all cancers in women and kills approximately 16,000 women annually. Though it is largely a disease of females, it is not entirely so, approximately two per cent being found in males. The reported average age varies from 50 to 55 years. It is conspicuously absent during adolescence and under the age of 20 years. Approximately 80 per cent of cases are encountered after the menopause.

Etiologic Factors

There is no more actual information available regarding the causation of mammary cancer among humans than there is regarding other forms of malignant disease, but at least some clinical observations suggest possible links in an as yet incompletely understood chain of events. Most of these observations point to the probable influence of hormonal stimulation. The absence of mammary cancer during the first two decades of life and its high incidence immediately following, during, and just preceding the menopause should be noted. The higher incidence among patients who have or have had chronic cystic mastitis, another hormone related condition, would also appear to be of significance.

The probable influence of genetic susceptibility must also be considered. It is not an unusual clinical experience to encounter families in which breast cancers occur startlingly often. There is probably no breast lesion which would be acceptable as a precancerous lesion. Yet clinical experience indicates that whatever underlying influences are operative in chronic cystic mastitis and in duct papillomatosis

Figure 1. Patient has a carcinoma of the left breast with visible skin attachment and nipple retraction. Simultaneous bulky sarcoma of the right breast.

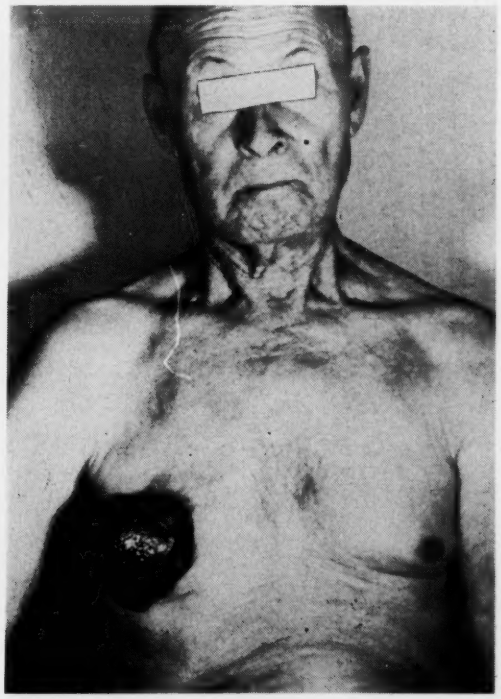

Figure 2. Large adenocarcinoma of male breast of 10 years duration.

certainly predispose the breast tissue to subsequent malignant change.

Clinical Pathology

Mammary cancer is a disease of the duct epithelium. It should be emphasized that Paget's disease of the nipple is but a clinical variant of this. The eczematoid nipple changes are but an outward manifestation of the underlying duct cancer. For the most part mammary cancer pursues a moderately active course. Abnormally rapid progress may be anticipated when inflammatory-like changes are present (inflammatory carcinoma).

In a small percentage of cases the activity of the cell seems to be largely directed toward intraductal proliferation with the accumulation of intraductal debris which may be expressed from the cut surface of the tumor in a comedo-like fashion. These comedo-carcinomas along with the mucinous carcinomas, which altogether make up less than 10 per cent of all breast cancers, may be expected to run a somewhat less aggressive than average course and to be more frequently curable. By and large, however, the clinical activity of histologically similar cases of the usual forms of breast cancer may vary very widely.

Symptoms and Signs

The common symptoms and signs of carcinoma of the breast should by this time be so well known as to warrant little attention. Several points may bear emphasizing. It is still too little appreciated, even among physicians, that pain is almost invariably absent in the patient with anything but advanced mammary carcinoma. Ulceration with infection, bone, nerve, or pleural involvement or swelling of the arm, secondary to massive axillary node involvement, may all produce pain, but curable cancer never does so. A "prickling" or "sticking" sensation may occasionally be mentioned, but actual pain is absent. Pain, in the presence of a lump in the breast, is presumptive though by no means conclusive evidence that the lesion is probably noncancerous.

Textbook accounts of the clinical setting of breast cancer are largely of academic interest only since they tend to stress the varied features of advanced cancer. If time is permitted to lapse until these have become manifest, all reasonable chance for cure has usually been lost. It cannot be emphasized too strongly that the only sign or symptom necessary for a presumptive diagnosis of breast cancer is a "lump in the breast." Any lump in the breast must be considered malignant until it has been microscopically proved to be otherwise. One of the most damaging statements that can be made by a physician to a patient who has a lump in the breast is that "You need not bother it, as long as it does not bother you." The "wait and see" policy has

Figure 3. Bilateral simultaneous mammary carcinoma of inflammatory type.

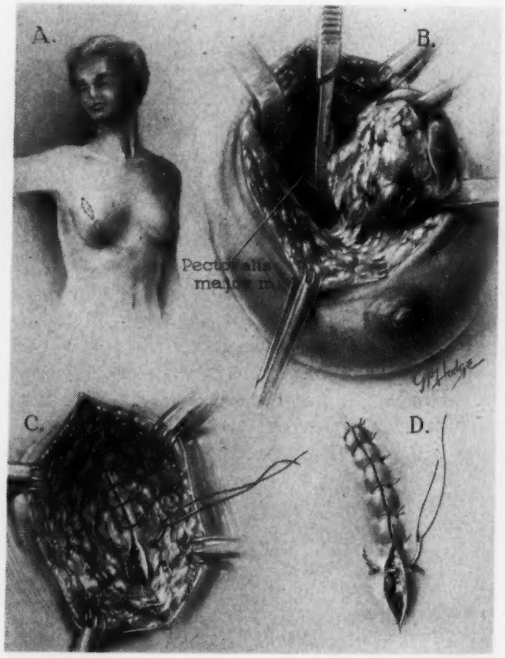

Figure 4. Technique of locally excising a breast tumor: overlying skin sacrificed, wide removal of grossly normal breast tissue, removal of pectoral fascia.

been practiced too often in the past. Patients who have previously had lumps removed which proved to be nonmalignant are no exception to the "cancer until proved otherwise" rule when new lumps appear.

Occasionally carcinoma may be present when no lump is palpable on breast examination. This most commonly occurs in Paget's disease. Here the eczematoid changes which begin on the nipple and slowly spread out concentrically over the areola will call attention to the underlying diffuse duct carcinoma. Occasionally, a small area of skin flattening or a very slight dimpling, appreciable only with the proper lighting arrangement, may be the sole hint to a small underlying carcinoma.

In the presence of a bloody nipple discharge, careful examination usually will reveal either a small mass or one area of the breast which, on pressure, causes the discharge to exude. In the absence of a mass, it is extremely rare to find a malignant lesion responsible for the blood, and somewhere under 50 per cent of patients with bleeding nipples have been found to have breast carcinoma.

Management of a Patient With a "Lump in the Breast"

Any patient presenting a "lump in the breast" should have it removed. The question, therefore, arises. What is a "lump in the breast?" In general, a breast lump has fairly well circumscribed borders. A fibroadenoma is a very well circumscribed tumor, usually movable in the breast substance. In cysts, areas of fibroadenomatosis and carcinomas, the borders become less distinct in the order mentioned and occasionally may be represented only by an area of thickening or, as mentioned above, an area of skin flattening. Under all such circumstances, the lesion should be considered carcinoma until proved otherwise.

The excision of a lump in the breast should be carried out in the operating room with preparations to proceed immediately with a thorough radical mastectomy if the mass proves to be malignant. It is fairly generally held opinion, with considerable statistical evidence to support it, that the five-year survival of the patient is considerably interfered with when a breast lump is diagnostically excised and a radical mastectomy is carried out a week or two later. One can only postulate that the vascular and lymphatic engorgement incident to the trauma and healing of the excision wound may play a part in the dissemination of either incompletely excised local disease or disease already present in the axillary lymph nodes.

Technic of Local Excision

Since in accomplishing the local excision of a breast tumor the initial consideration is that the mass may be a cancer, the entire technic should be based on this possibility. The patient is therefore draped as for a radical mastectomy. Cosmetic incisions have little place in the management of breast cancer. This does not imply that they may be entirely forgotten, but cosmetics may only be considered when no direct sacrifice to easy exposure and incision of the suspected tumor is imposed. In general, a skin incision which leads most directly to the tumor is best.

The direction of the incision should be planned

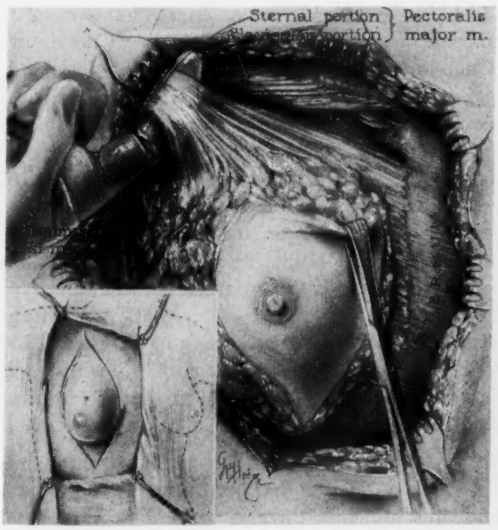

Figure 5. Radical mastectomy: commonly used eliptical incision (insert); lateral and medial flaps developed; humeral attachment of costal portion of pectoralis major muscle being freed.

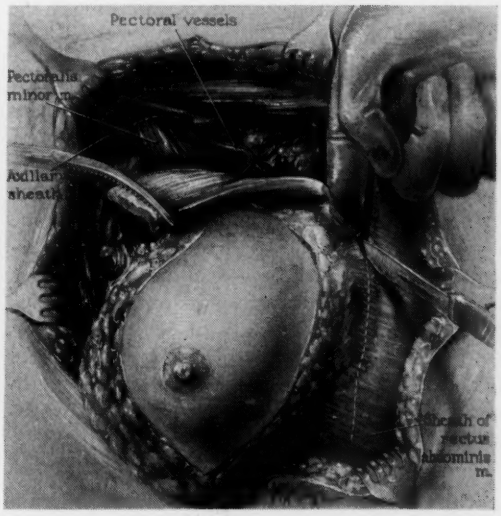

Figure 6. Radical mastectomy: costal attachments of pectoralis major muscle being cut; perforating branches of internal mammary vessels are secured at this point.

to accommodate as nearly as possible the subsequent radical mastectomy. When tumors lie close to the skin, a skin elipse of varying width should be excised along with the underlying breast tissue to avoid cutting through involved dermal lymphatics. The tumor itself should be excised widely, inclusive of all underlying breast tissue and pectoral fascia. This will accomplish removal of adjacent lymphatics which may be permeated for short distances by carcinoma as well as the primary draining lymphatics which proceed to the pectoral lymphatic trunks.

It appears to make little difference whether the excision is accomplished with the endotherm knife or ordinary scalpel. Advocates of the former method seem unable to demonstrate any better five-year survival rates. Haagensen has proposed incising rather than excising tumors. In our own experience tumors large enough to be incised cause little trouble in making a diagnosis. Having frequently found small areas of carcinoma incorporated in larger masses of mastitis, it has occurred to us that the carcinoma might frequently be missed if such a purposed technique were routinely employed. In general, we have chosen wide excision as the most generally applicable diagnostic procedure.

The surgeon seeing large numbers of breast cancers will be able to determine in approximately 80 per cent of circumstances whether he is dealing with a carcinoma by the gross appearance of the cut specimen. Not infrequently the pathologist will also be unwilling to make an immediate commitment on his examination of a quick section, but will wish to await a more carefully prepared paraffin section.

Simple Mastectomy

Strictly speaking, this includes only simple removal of the breast. However, it would seem that one should include under this heading every procedure which falls short of being a radical mastectomy: the removal of the breast with low axillary nodes; the removal of the breast with a portion of the pectoralis major muscle and a part of the axillary contents; et cetera. These are all compromise procedures and should be employed only when some definite, positive contraindication to radical mastectomy exists. The absence of palpable axillary nodes is no indication for simple mastectomy, for microscopically positive nodes are nevertheless present in 30 to 50 per cent of all such cases. We have felt it necessary to resort to simple mastectomy in seven of 500 breast removals for mammary carcinoma.

Radical Mastectomy

This anatomic dissection described almost simultaneously by Halsted and Willy Meyer is technically not easy if one wishes to accomplish it properly. Though it is seldom realized, more technical experience is required in the accomplishment of a thorough radical mastectomy than in the performance of the average subtotal gastrectomy. The more striking difference between the immediate postoperative mortalities of the two procedures has somewhat overshadowed this fact. In addition, there can be little question but that more is lost in the execution of an inadequate or poor radical mastectomy for breast cancer than in a mediocre gastrectomy, partial or total, for carcinoma of the stomach. This becomes apparent when one realizes that a properly executed radical mastectomy will save approximately five times as many patients as a well executed gastrectomy.

The skin incision should suit the individual case. In general, the oblique or vertical elipse (Willy Meyer) will be most frequently applicable and provides excellent axillary exposure. For markedly pendulous breasts the transverse eliptical (Stewart) incision is useful. However, it tends to make exposure of the upper axilla somewhat more difficult. The arrowhead (Greenough) incision is indicated whenever wider removal of axillary skin is desired, as when a primary is located superficially in the axillary portion of the breast or when an involved low axillary node is attached to the skin. Incisions which tend to leave angular skin flaps are to be avoided since the points will often undergo necrosis. Under no circumstances should a radical mastectomy be planned under a specified incision nor should a tumor area be closely approached in order to conform to any certain incision.

The question is often asked, "How much skin should be removed adjacent to the tumor?" An anatomic description of the lymphatics of the breast is not intended here, but the answer to the above question is pertinent to them. The primary lymphatic drainage of the breast is deep into the axillary and pectoral lymphatics. Retrograde lymph flow into the skin lymphatics in tumors not directly involving that structure takes place as a rule when the primary lymphatic routes are blocked. Therefore, if one takes at least as much skin about the tumor in centimeters as he is able to go around the tumor in depth to the chest wall, he will as a rule have taken a sufficient amount. The conventionally stated 2.5 to three cm., or two to three finger breadths may not be nearly adequate. One should never take less skin than is indicated but should plan to close the defect with a split graft if necessary.

If the skin incision has been made in conformity with this principle, there is no need to dissect extremely thin skin flaps, but they may be dissected in a graduated fashion, thin at the line of incision,

progressively thicker as their bases are reached. This assures them a better blood supply and decreases the incidence of flap necrosis. The lateral flap is carried back to a point about 2.5 cm. posterior to the anterior border of the latissimus dorsi muscle.

Dissection of the medial flap proceeds to the sternal midpoint. Inferiorly, the costal margin limits the dissection and, superiorly, the junction of the sternal and clavicular portions of the pectoralis major muscle. This anatomic division, though usually visible, can readily be developed by gently inserting the finger into the muscle at the costoclavicular joint where these muscular divisions converge. This intermuscular plane is developed laterally to the humerus. The sternal portion is then detached from the crest of the greater tubercle of the humerus and retracted medially and inferiorly.

There is no need to remove the clavicular portion of the pectoralis major muscle since it does not interfere with exposure of the axillary vein and obscures no lymph nodes draining the breast. Just below the costoclavicular joint the finger may be inserted into a readily identifiable cleavage plane beneath the sternal attachments of the pectoralis major muscle. The origin of this muscle is severed without traction. It is here that the perforating branches of the internal mammary vessels with their lymphatics are encountered, clamped, cut and ligated. Those in the second and third interspaces are usually the largest of the group.

Again considering momentarily the lymphatics of the breast, drainage is primarily by way of the external mammary (axillary) and internal mammary routes. Though the external mammary group is the larger of the two, it has interposed along its course an elaborate node filter system (axillary lymph nodes). The internal mammary lymphatics lack such a system until they have entered the chest. For this reason it has seemed logical to section the internal mammary group first, supposing that cells lying within the local lymphatics occasionally may be shaken free during the operation.

The costocoracoid membrane (coracoclavicular fascia) is next divided, thereby exposing the pectoral vessels and nerves. These are divided and ligated. The scapular insertion of the pectoralis minor is next detached close to the coracoid process. It contains a small nutrient artery at this point which usually requires ligation. Part or all of the pectoralis minor may then be detached from the chest wall as desired. Excellent exposure of the entire axilla is thus obtained. The anterior axillary fascia is incised over the large nerve trunks to the upper extremity and the axillary vessels. Gentle traction and sharp dissection are all that is needed to complete the exposure of the axillary vein to its inferior border.

Beginning at the costoclavicular ligament (a tough, sharp, readily identifiable structure), another areolar tissue sheath, the posterior axillary fascia, is incised and a plane is entered which extends laterally, anterior to the external intercostal and serratus anticus muscles to the scapular and latissimus

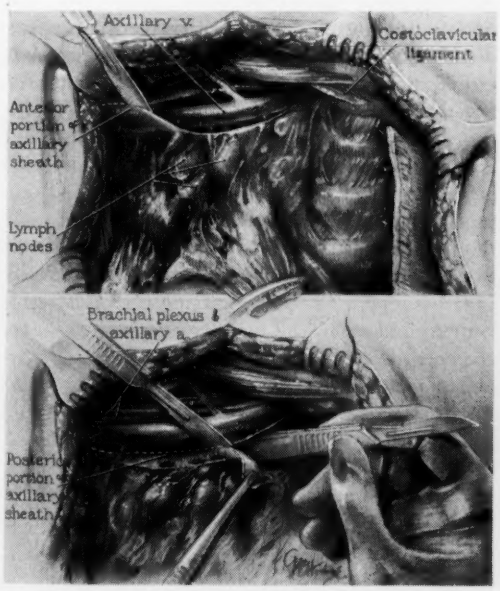

Figure 7. Radical mastectomy: the insertion of the pectoralis minor muscle has been cut; above, the anterior layer of the axillary sheath is being incised, sharp dissection is used; below, the posterior layer of the sheath is cut. The dissection should begin at the costoclavicular ligament.

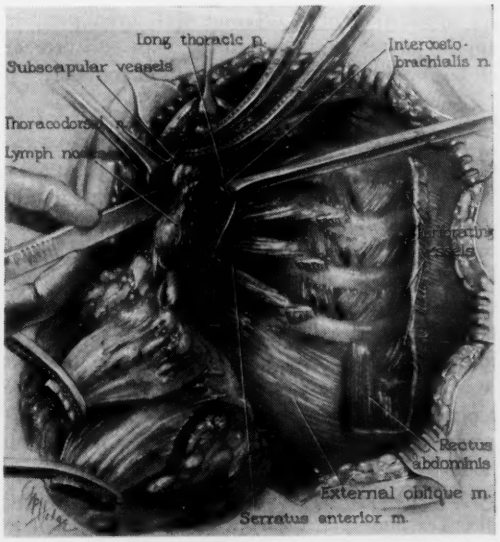

Figure 8. Radical mastectomy: as the axillary contents are swept laterally, the long thoracic nerve is found within the posterior axillary sheath; the thoracodorsal nerve is located just medial to the subscapular vessels; the subscapular fascia is divided high above the vein freeing the axillary contents.

dorsi muscles. The axillary contents are contained within this fascial envelope, which is then freed from the axillary vein in a downward, lateral direction by ligating tributaries of the axillary vein as they are encountered.

The axillary vein may be removed without the development of appreciable arm edema in most cases if lymph nodes are adherent to it. The nerve to the serratus anterior muscle is found partly within the posterior areolar sheath described, and may readily be dissected free and should be carefully spared. Injury to it produces winging of the scapula. The nerve to the latissimus dorsi is somewhat more difficult to find but usually is encountered just medial to the subscapular vein. When any extensive low axillary node involvement is present, this nerve should be sacrificed rather than risk tumor dissemination by dissecting it free.

Care in the dissection of the axilla is probably the most important part of a radical mastectomy. Adequate exposure of this entire area cannot be obtained unless the entire costal head of the pectoralis major muscle is removed. Blunt finger or gauze dissection or the use of rake-like instruments to expose the axillary vein tributaries are to be discouraged since they unquestionably disseminate cancer cells.

Following removal of the breast the wound is well lavaged with saline to remove fatty debris. A drain is placed through a stab wound in the lateral flap up to the axillary vein and the flaps are apposed. If this cannot be done, they are sutured to the chest wall and a split thickness graft is applied. The careful application of a dressing with even pressure applied in the axilla and to the flaps will prevent all but occasional serum pockets from forming.

General Considerations

Nitrous oxide induction followed by ether-oxygen is a very good anesthetic in radical mastectomies. Patients may be kept in the first phase of the third stage of anesthesia since complete muscular relaxation is not required. By actual measurement the average patient will lose at least 500 cc. of blood during such a procedure. Coller and co-workers in a collected series found the average blood loss at radical mastectomy to be 732 cc. In many instances it is advisable to transfuse during the operation to replace this blood loss. With such a large wound exposed to contamination from the air for several hours, it is important to work with as little conversation and as gentle handling of tissues as possible. Traction upon the pectoral muscles incident to their removal will often precipitate shock.

Complications

The complications of radical mastectomy are as a rule of minor degree. Serum pockets and infections, either as a result of undiscovered serum collections or secondary to skin necrosis, make up the majority. Pneumothorax resulting from punctures of the intercostal spaces and air embolism caused by injury to the axillary vein have been reported but have not occurred in our hands. Any of the complications peculiar to a major surgical procedure done on elderly patients may occur. Shock may result from blood loss and excessive traction unless care is exercised.

We have had only four deaths in well over 500 mastectomies. One of these was due to cardiac failure, one to pulmonary embolism, one to uremia, and the fourth was due to a wound infection followed by bacterial endocarditis. In some respects the low mortality attending radical mastectomy has been a deterrent to the cure of breast cancer for it has, in instances, attracted those to attempt the operation who are not entirely familiar with its meticulous accomplishment. It must be remembered that the chance for cure of the patient whose disease still remains localized to the breast and axilla lies in the surgical treatment alone, and that an enormous responsibility is thereby imposed.

Irradiation

There is no question but that carcinoma of the breast should be radically removed if no contraindications to such treatment exist. Whether this should be preceded or followed by roentgen therapy, however, has given rise to considerable controversy. It is now quite generally agreed that preoperative irradiation has little place in the treatment of mammary cancer. It is still contended by a few that improved five-year results may be obtained by the use of postoperative therapy to the surgical field, though this is highly disputed. Many of these improved results have taken place during more recent years and may probably be more correctly ascribed to earlier diagnosis. In the treatment of locally advanced disease in which surgical removal cannot be accomplished, Lenz has reported highly gratifying results. Patients with metastases to the lungs, pleura, mediastinum, abdomen, liver and brain are not benefitted by irradiation but are, in fact, often made more ill by the treatment.

There is no question of the real palliative value of irradiation in the treatment of skeletal metastases. For some reason, as yet unknown, breast cancer in bone is quite sensitive to moderate roentgen ray dosage and is almost invariably followed by gratifying relief of pain and with recalcification of the involved bone.

Endocrine Treatment

This has been either in the nature of castration,

surgically or radiologically produced, administered either prophylactically or therapeutically, or by the direct use of hormone therapy, both estrogenic and androgenic, usually used therapeutically only. The entire subject is difficult to evaluate, and many conflicting reports may be found. There seems to be a fairly uniform agreement, however, that either x-ray or surgical castration is frequently of benefit to premenopausal women, especially young women and those who are either pregnant or lactating at the time the carcinoma is discovered. The therapeutic value of castration appears to be greater among patients with skeletal metastases with benefit obtained in approximately one-third of the patients treated. Dramatic regression of extra skeletal metastatic disease has also been occasionally reported following castration alone.

Summary of Direct Hormonal Treatment

It would appear that androgen therapy is more effective in premenopausal women and that stilbestrol is more effective in postmenopausal women with either skeletal or soft part areas of involvement. The best results from stilbestrol have been reported in elderly women after the age of 65. Enhancement of the effect of irradiation on mammary carcinoma has also been reported in patients simultaneously receiving stilbestrol, and we have noted this also.

Administration of testosterone to males with mammary cancer often produces dramatic regression, to the point where some have advocated this as a reasonable substitute for mastectomy. Unfortunately, however, the results of hormone therapy are not lasting and experience is heralding that already obtained in prostatic carcinoma. The patients who appear to be least of all affected by hormonal therapy are those women at or about the menopause. The results of any form of endocrine treatment among them have been very disappointing.

Prognosis and End Results

The outlook for cure in mammary carcinoma is based entirely on whether or not the patient is operable. No inoperable patient will be cured. Hence, this aspect of the problem is related closely to the criteria of inoperability. Most of these criteria are now well known. A patient will not be cured by radical mastectomy and, therefore, should not be operated on who: (1) has distant metastases, (2) has supraclavicular node metastases, (3) has an inflammatory type of carcinoma, (4) has satellite nodules in the skin over the breast, (5) has extensive edema of the skin over the breast or edema of the arm, both of which indicate that the lymphatics are involved to the point of being solidly plugged, (6) has parasternal or intercostal tumor nodules.

Other less ominous but prognostically poor signs are: (1) ulceration of the skin, (2) limited edema of the skin of the breast, (3) fixation of the tumor to the chest wall, (4) large and numerous fixed axillary lymph nodes, (5) pregnancy or lactation.

The end results of any form of treatment in breast cancer must be compared to the survival in untreated cases. Approximately 20 per cent of patients with mammary cancer untreated throughout their entire course will survive for five years. Approxi-

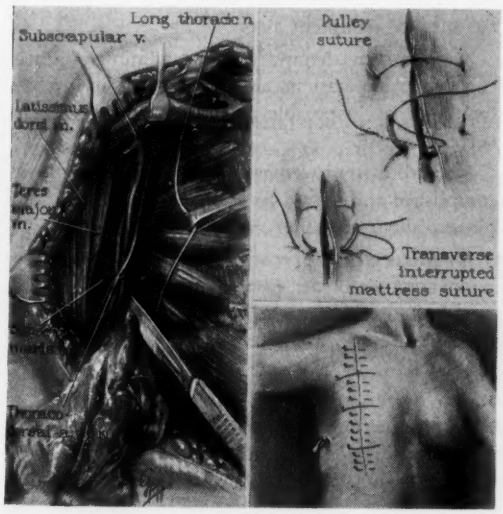

Figure 9. Radical mastectomy: completion of the dissection with both nerves preserved intact. The flaps should be apposed under moderate tension with pulley sutures. A drain is placed from the axillary region out through the lateral flap (lower insert).

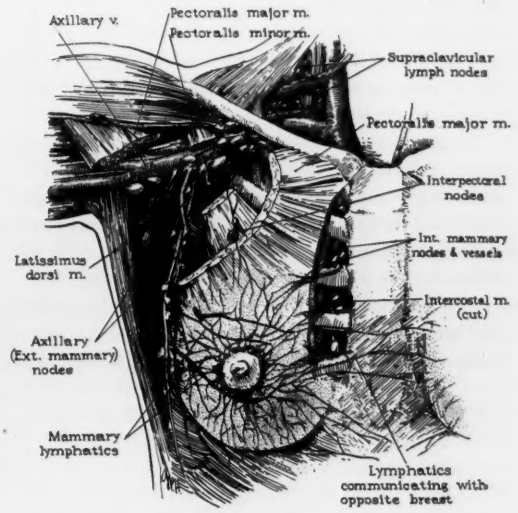

Figure 10. Lymphatic drainage of the breast shows that the internal mammary nodes as well as the axillary nodes represent primary echelon draining areas. Both should therefore be removed if true cancer surgical principles are to be followed.

mately five per cent will survive untreated for as long as 10 years.

Recent reports indicate some improvement in five-year survival to about 50 per cent of all patients operated. About 75 per cent of those having no lymph node involvement may be expected to survive five years. About 40 per cent of those having involvement of axillary lymph nodes may be expected to survive for this same period. Most of the patients dying of disease after five years originally had axillary node involvement.

Future Improvements

With the encouragement derived from the more recent aspects of direct hormonal therapy of breast cancer, one can hardly be considered naive for entertaining the thought that eventually some substance, metabolic or otherwise, may be uncovered which will either permanently control or possibly eradicate all mammary cancer. Until such a day arrives, however, there are two courses for immediate improvement available to us.

The first is derived from earlier diagnosis and can readily be assessed when one reflects that the average delay before treatment is applied for with this type of tumor which appears externally and can be readily felt by both the patient and her physician, is still approximately 12 months. This delay is reflected in the fact that approximately 50 per cent of patients appearing for treatment are inoperable and that of those who are operable, axillary metastases may already be found in a little more than 50 per cent. Obviously the answer to this is education of the patient and her physician. Insofar as the education of the patient is concerned, women may easily be instructed in the routine careful examination of their breasts for lumps. The patient and doctor alike must learn that all lumps in the breast past the age of 20 must be considered malignant until proved otherwise.

Surgery of breast cancer can probably not go much farther. Some have recently undertaken to re-evaluate the possibilities of combining supraclavicular lymph node dissection with radical mastectomy. This field was originally explored by Dr. Halsted with no five-year survivals resulting.

Our own attention has recently been attracted to the removal of a portion of the internal mammary node chain in continuity with the breast and with the contents of the axilla (external mammary node chain), and we have been surprised to find a number of these primary echelon nodes involved in patients who presented an entirely operable form of mammary cancer as measured by the criteria above mentioned. In other words, we have certainly learned one cause for our failures to cure some patients previously operated on by a mastectomy of the usual "radical" sort. Whether or not the routine entering of the chest and the removal of this node chain will add appreciably to five-year survival remains to be seen. We believe that it will and that a re-evaluation of the surgical accomplishments in mammary cancer must eventually be made on that basis. Only the future will tell.

Summary

1. The clinical features of mammary cancer have been discussed with emphasis on those which are of practical importance for earlier recognition of this condition.

2. Undelayed operating room confirmation of any suspected lesion followed by immediate radical mastectomy remains the unquestioned treatment of choice. Excision of breast cancers followed later by radical mastectomy seems to impair the patient's opportunity for cure.

3. The operative management of a suspected patient is presented with a description of the technique of a thorough radical mastectomy based on over 500 personally done or supervised cases. Simple mastectomy and compromise "radical mastectomy" have very little place in the treatment of breast carcinoma. It must be realized that success in curing the patient with localized disease is dependent on the surgical treatment alone.

4. Roentgen therapy and the administration of endocrine preparations are valuable adjuncts to the treatment of inoperable cases or of those with recurrent disease.

5. Future improvement will undoubtedly be accomplished and should be easily possible by the simple expedient of earlier diagnosis.

6. A surgical approach involving the en bloc removal of the breast, pectoral muscles, axillary contents and internal mammary node chain offers promise of future improvement but remains to be further evaluated.

Tracer Research and Cancer*

John H. Lawrence, M. D.

Berkeley, California

Progress in the treatment of cancer appears to me to be extremely slow. We still have to rely on early diagnosis and treatment with surgery and radiation. During the last 10 years there has actually been very little progress in the means of treatment, except insofar as methods of surgery and radiation have improved. Additional exceptions are the few examples of hormone therapy which Dr. Sugarbaker has mentioned, and the very limited number of instances in which some of the artificial radioactive elements are adding to the armamentarium of therapy. Hence various government and private agencies support cancer research in the hope that it will lead to better understanding of this disease and that better understanding may eventually lead to improved methods of therapy.

Rather than discuss in detail one investigation which is going on in my own laboratory, I would prefer to give you a few examples of the use of tracers in the development of our understanding of cancer. Even though these may be of negligible importance to you as clinicians and to us in research at their present stage of development, these represent examples of ways in which the problem is being attacked.

By means of tracer techniques various substances are labeled with radioactive isotopes, either in simple compounds or inorganic compounds or in the form of labeled hormones, amino acids, or cancerogenic hydrocarbons. By placing counters over the body either of animals or man, these materials may be followed in their course through the organism and the amount of material at any given point may be measured. Another technique for the same general purpose involves taking samples of the various tissues, fluids, or gases and measuring the amount present following the administration of a tracer dose. Extremely small doses of radioactive materials are used in this type of study—doses which are entirely safe, and indeed very little above the amount of radiation you are receiving here in this room now, in the form of cosmic rays and radium in the walls of this building.

In order to illustrate how a tracer can tell you something about the growth of normal and abnormal cells, let us describe a simple experiment in phosphorus metabolism. If we compare the amount of phosphorus in a normal lymph node with a lymph node infiltrated with tumor cells, we find that the amount of phosphorus per gram is approximately the same. Thus, you can not distinguish between a neoplastic and a normal lymph node by measuring the total amount of phosphorus that is present. If, however, you administer in each case a dose of sodium radiophosphate, the difference becomes apparent. Comparison of the amount of phosphorus present in the lymph nodes and livers of normal and lymphomatous mice, as calculated on the basis of ordinary phosphorus, shows that the values are approximately equal in the lymph nodes of normal and tumor animals, and approximately equal in the livers of normal and lymphomatous animals. By contrast, it is seen that a difference exists between the labeled phosphorus uptake in these two conditions when radioactive phosphorus is injected into the animal. When the radioactive isotope is used, the lymphomatous lymph node takes up an enormous amount of phosphorus, whereas the normal lymph node absorbs very little. As also shown, if the phosphorus uptake is studied for a period of seven days, it will be seen that the phosphorus has primarily gone into the nucleoprotein phosphorus; that is, the phosphorus participating in the building of cell nuclei.

Recent work by two of my colleagues, Dr. Lola S. Kelly and Dr. Hardin B. Jones, is directed toward the breakdown of the fraction of tissue into which this phosphorus goes. Ordinary inorganic phosphorus, when administered to animals, enters many different tissues and compounds in the body including nucleic acids. Particular interest in this research is directed to so-called desoxypentose nucleic acid, which is an important organic nucleic acid having to do with cell multiplication. Phosphorus given to animals bearing a small subcutaneous mammary tumor is very rapidly synthesized into desoxypentose nucleic acid. Phosphorus comprises one of the atoms in the complex molecule of the labeled nucleic acid. The rate of synthesis of the labeled nucleic acid in the normal liver of these animals is very high, just as it is high in the tumor. In a group of normal control animals, the turnover of phosphorus in the desoxypentose nucleic acid is normal; but a tumor weighing as little as 84 milligrams immediately influences the specific activity of the phosphorus resulting in a high turnover rate in the normal tissues. This indicates that the presence of a tumor influences the metabolism of other tissues, even though the other tissues be histologically normal. Cancer patients are now being tested by taking their sera

* This is a stenotypic transcription of Dr. Lawrence's talk which was given with lantern slides.

to determine whether the factor which causes this stimulation of nucleic acid metabolism in normal tissues can be isolated.

In connection with this phase of our work, the chemists in our laboratory have synthesized radioactive tyrosine. This very important amino acid is labeled with radioactive carbon; while it is like ordinary tyrosine chemically, its course in tissue may be followed and measured by the Geiger counter. Since tyrosine is used in melanin formation, it is conceivable that tyrosine fed to mice might concentrate in the melanosarcomas. Although it seemed unlikely that such concentration would be found, the labeling of the material gave opportunity to learn something about tyrosine metabolism. Dr. Charles Heidelberger and Dr. Hardin Jones have published the results of some of their work on tyrosine metabolism in the Journal of Cancer. An interesting highlight of their findings is that when tyrosine was given to mice carrying melanosarcomas, high concentrations of the material did enter the melanosarcoma; but high concentrations also entered the thyroid gland and the adrenals, because tyrosine is not only a precursor of melanin but also a precursor of adrenalin and thyroxin.

Two of my associates have done considerable research on the mechanism of cancer induction in mice through the introduction of labeled dibenzanthracene and methylcholanthrene. Stilbamidine and labeled glucose are also being studied; and a project on cholesterol metabolism is being carried on under the supervision of Dr. John Gofman, not only because of its probable importance in relation to cancer but also because of its obvious significance in atherosclerosis.

In connection with the work with stilbamidine, analysis of the tissues of patients with multiple myeloma, to whom stilbamidine has been given, reveals a tremendous concentration of the stilbamidine in the liver even though the liver is not infiltrated with myeloma cells. A group of experiments were run, chiefly by Dr. John Weaver, to determine why this was true. Radioactive stilbamidine was given to both normal and tumor mice in each of several strains: the A, DBA, C57 and C58 strains. After administration of the radioactive material, analysis of the livers of animals of the A strain carrying even a small tumor revealed a very great concentration of stilbamidine, as compared to an equal group of normal animals. Here then is another example of the remote effect of a small tumor elaborating a humoral substance which stimulates the liver to take up the stilbamidine. We know from previous work, particularly by Snapper, that stilbamidine does complex with nucleic acids.

Another example of a labeled organic acid is brought out in some work using labeled amino acids and organic acids labeled with Carbon-14. Animals are given intravenously a small tracer dose of a labeled organic acid and placed in a small metabolism chamber. All of the carbon dioxide which they exhale during a given period is collected and measured. Actually, the CO_2 is absorbed by sodium hydroxide, precipitated as barium carbonate, and this barium carbonate, which contains the radioactive carbon, is filtered and measured under the counter. The excretion curves after the single dose in normal and cancer animals are similar for most of these labeled organic acids. However, when labeled proprionic acid is used, the cancer animals are distinguished from the normal animals by their different rate of excretion of the amino acid in their exhaled air. In this connection it may be observed that our lack of definite knowledge about growth is demonstrated by this problem. Doctor Jones who has been working with this and other labeled acids for about two years is unable to explain the mechanism of this difference. He knows that the breakdown of this labeled material to carbon dioxide and water goes through a different series of stages in the normal animal compared to the tumor animal. The metabolic pathway is different and it is again an example of the remote effect of the small tumor on the general metabolism of that animal. These last three examples are all possible cancer tests and they are now being studied from that standpoint with human serum, with the possibility in mind of finding a humoral agent which will, when injected into animals, produce these measurable changes.

Radioactive cobalt is also valuable as a tracer in the study of normal and abnormal growths. Indeed, the first reliable information on the distribution of cobalt in mice, which causes red cell hyperplasia, has been obtained through its use, since the cobalt can be measured in extremely small quantities in contrast to the difficulty of measuring by microchemical methods. An example of the sensitivity of the method is that as little as two micrograms of cobalt per gram of wet tissue are measured in the mouse liver. The animals are caused to develop a marked polycythemia by chronic cobalt administration; then through measurement of injected radio cobalt, the localization of this element is determined in the various tissues. A fairly high concentration of the cobalt was localized, for instance, in the bone marrow, the site of the red cell hyperplasia. A tremendous polycythemia may be produced by daily injections of cobalt; the red cell count may be as high as from 10 to 17 million.

By means of another technique it is possible to measure as little as one ten-billionth of a gram of an

element in a gram of tissue. We are discovering that there are many trace elements in the body that we had not known were present. There is, for example, gold in the normal animal and in the tissues of the normal human subject. This technique developed by my colleague Dr. Cornelius A. Tobias, consists of taking a sample of blood or tissue, ashing it, and placing it in the atomic pile. Neutrons cause many elements in the sample to become radioactive. The material is then returned to the laboratory and measured for radioactivity, after so-called carrier materials have been added. If one is interested in the possibility that there is a small amount of cobalt in a given tissue, one adds a large amount of carrier cobalt to the sample and precipitates all of the cobalt including that which has been rendered radioactive by induction in the pile. The total sample is measured for radioactivity, and the amount of cobalt which was there before the carrier material was added is calculated from the total induced radioactivity. Elements such as scandium, manganese, zinc and gold have been found in normal tissues by using this technique. Thus a technique has been devised for tracing elements in tissues which is more sensitive than any microchemical method ever used, in the case of many elements.

Labeled material can also be followed by the multiple counter technique. As many as three counters are used over a small animal and four or more over the various parts of the human body. The counting rate is recorded on a revolving drum. In a typical study, one counter may face the thigh, another the liver, and a third the heart. Following the injection of labeled compounds and labeled inorganic materials, the experimenter can get a moving picture of the passage of labeled materials through the body, in terms of site of deposition and rate of movement.

Many investigators, using radioactive iodine, have worked out the classification of goiters and thyroids by the percentage of uptake of the iodine measured by the *in vivo* technique. High uptakes are consistently found in hyperthyroidism, medium uptakes in the normal thyroid, and low uptakes in the myxedematous subject. This widely discussed test may now be done with as little as five mc. of iodine, due to the development of the scintillation counter. Previously it was necessary to use 100 mc. I-131; one of my objections to this test was based on the fact that one does not like to give these high dosages to normal individuals. Now that the scintillation counter, with its much greater sensitivity, is available, we do not object to the thyroid function test with radioactive iodine any more than we do to a basal metabolic rate test, since it is now possible to do it with a small dose of the tracer.

Studies with radioactive iron and radioactive carbon are being carried out, both *in vitro* and *in vivo*. It will be recalled that the body contains normally about three grams of iron, chiefly in the form of red cell hemoglobin; about two and a half grams of the iron is in the red cells, the rest being in other tissues. Four isotopes of iron occur in nature—not radioactive isotopes, but isotopes having varying atomic weight while all are chemically iron. The iron which the clinician uses in the treatment of patients consists of a mixture of such isotopes. Iron may be made radioactive in the cyclotron or in the atomic pile; that produced in the cyclotron has the advantage of a short half-life (47 days)—an important factor since iron is not excreted. The cyclotron-produced iron emits both electrons and gamma rays which have enough energy to permit the measurement of iron movement through the body by placing counters over the living subject.

Studies by my associate Dr. Rex Huff and others with radioactive iron have led to the development of a bone marrow function test now used routinely by us. Within four hours it is possible to measure the rate at which a patient is making red cells; this is important to the handling of many medical conditions and will eventually be as readily available as other clinical laboratory tests. A single dose of iron, perhaps five micrograms containing 10 microcuries of activity (a safe tracer dose) is injected intravenously; samples of blood are withdrawn at half-hour intervals and measured for activity. In the normal patient, the plasma iron gradually decreases with time in a straight line plotted logarithmically; whereas patients with polycythemia vera, who made red cells very rapidly, show an abrupt fall in the amount of plasma iron, and patients with aplastic anemia show a very slow clearance of the iron from plasma. In tracing the route of this iron, a counter placed over the head of the femur shows that as the iron disappears from the plasma it enters the marrow directly, at the same rate that it leaves the plasma; at the end of 10 to 15 days, nearly 100 per cent of the iron has entered the red cells. From such a dynamic picture of red cell production it is possible to determine the number of milligrams of iron used in making red cells per 24-hour period, or the per cent of hemoglobin renewed per day. Normal individuals have been shown to renew about .85 per cent of their hemoglobin per day. This correlates with the known life span of the red cell—normally approximately 120 days. In polycythemia vera, the rate of renewal is as high as three or four per cent per day. It was surprising to learn that some patients with leukemia also manufacture red cells at a rapid rate. In a study of about 75 patients with leukemia, a normal or increased rate of pro-

duction was almost uniformly found. We therefore suspected that in both polycythemia and leukemia the life span of the red cell is less than normal, and in leukemia, it must be markedly less since the leukemic patient is often anemic in spite of a normal red cell production rate. In cancer also, we found an indirect effect upon red cell life which may account in some cases for the anemia of cancer.

A direct approach to the problem of red cell life span in cancer involves the use of glycine labeled with Carbon-14, in animals and man. This amino acid enters the hemoglobin molecules and remains there as long as the red cell lives. Weekly samples of blood show the same rate of activity until the death of the cell. In normal blood, the life span of the red cell as studied by this method was shown to be about 120 days, confirming earlier findings; leukemic and polycythemic patients, however, have been shown by this method to have red cells with a short life duration. The anemia which occurs in several clinical conditions has thus been shown to be due not to the failure of red cell production but to the curtailed life span of the erythrocytes. This is an example of the changes produced by cancer in animals and in man.

The problem in polycythemia vera is not one of typical cancer, but rather of abnormal growth; and as we are trying to learn more about growth, we have made numerous studies of the various types of polycythemia, including the polycythemia of altitude. During February and March, 1950, we made a study in Peru of the effects of altitude on hematopoietic activity. We set up a laboratory, using the facilities generously lent us by Dr. Alberto Hurtado, of the Academy of Medicine, Lima, at each of two places: one at Lima, which is at sea level, and one at Morococha, which is at 14,900 feet. Studies were made on normal subjects living at sea level, both in their natural habitat and after acclimatization to altitude; on other subjects with the polycythemia of long duration at high altitude, both in their native habitat and at sea level; and on patients with altitude polycythemia combined with silicosis resulting from work in the mines. Some of the latter had polycythemias resulting in red blood counts as high as nine million cells per cubic millimeter. We were interested in comparing the "neoplastic" type of polycythemia vera with so-called environmental polycythemia. The hematocrits were as high as 83 per cent; the blood so viscous that it had to be withdrawn with No. 16 needles and then with difficulty. The hands and skin color showed extreme pinkish cyanosis, due to the great mass of red cells in the capillaries.

A group of medical students from the University of San Marcos, Lima, served as our experimental subjects representative of persons living at sea level; miners from the Cerro de Pasco mines served as representatives of individuals living at 14,900 feet. Iron metabolism studies showed an immediate increase in red cell production due to anoxia on moving to altitude from sea level. A striking effect of anoxia on growth and an immediate decrease in red cell production on descent from altitude to sea level were observed as the effect of increasing oxygen tension in the atmosphere. The effect on iron metabolism of an increase in available oxygen is such that in a subject moving from altitude to sea level the decrease parallels that in a patient with aplastic anemia.

A study of the movement of iron *in vitro* reveals that in normal subjects over 90 per cent of the iron enters the red cells; in a patient with aplastic anemia, the iron leaves the plasma but does not concentrate in the red cells. In one case of aplastic anemia, for example, only one-tenth of the iron may go into red cell production.

In vivo studies of normal subjects and patients with abnormalities of erythropoiesis have been made by Huff and associates by placing a counter over the sacrum, which contains the largest mass of marrow in the body, and also over areas such as the liver and spleen. In one polycythemic patient with a hypoplastic marrow, the red cells were being produced in the spleen as evidenced by these iron studies. In the normal subject, the curve of uptake of radioactive iron rises as a function of time; but in the patient with extramedullary hematopoiesis, no such rise occurs within the sacrum. A patient with anemia revealed a hypoplastic marrow and hypersplenism. The iron disappeared from the blood, entering the liver to some degree but chiefly the spleen. Practically all patients with myelogenous leukemia produce their red cells in the spleen and liver, the sacrum taking up no iron and thus producing no red cells.

A localization study of the uptake of iron by various parts of the body enables us to classify individuals according to the site of red cell production. The normal subject has the largest uptake at the sacrum, which is the site at which the largest amount of marrow is normally concentrated; in aplastic anemia the sacral marrow typically reveals a very small red cell production and a high concentration of the iron in the liver; the polycythemic produces many erythrocytes in the spleen, as shown by the high uptake of iron in the spleen; the myelogenous leukemia patient produces few red cells in the marrow but concentrates the iron and the red cell production in both liver and spleen. In this way growth rates and sites are being measured—that is with reference to red cell production.

In conclusion, with the microscope it is possible to see cells; with the radioactive isotopes, used as tracers, it is possible to begin to learn what is going on within the cells. The technique is powerful. Through the use of tracers in organic compounds, I believe that gradual progress will continue to be made in the understanding and treatment of cancer.

The Diagnosis of Accessible Cancer

Danely P. Slaughter, M.D.

Chicago, Illinois

The title of this presentation was chosen deliberately to highlight the fact that most cancers affecting the human body are accessible.

The diagnosis of cancer is not actually a difficult problem. To every one of us practicing medicine, it is essentially a matter of physical examination, using the aids of instrumental examination that are available to us and having a high index of suspicion for any given lesion. The final diagnosis of cancer depends actually on a biopsy, and that is one of the simplest maneuvers that we can do. I think the AMA fracture manual has the motto "Splint them where they lie;" in cancer, it is biopsy as the first thought, and it is a simple maneuver and frequently does not even require local or topical anesthesia.

Now I said that most cancers affecting the human body are accessible, and I mean this in the sense that they are visible to the naked eye, palpable, or within finger reach of palpation. If you add to that the cancers that can be visualized with instruments which do not have optical systems (such as the proctoscope), the percentage increases; and if we add those that are visible by use of the cystoscope, gastroscope, and bronchoscope, eliminating the x-ray, you will find that about 85 per cent of cancers that affect humans are accessible. They should not be a difficult problem in diagnosis; any one of us can do it and it doesn't require numerous consultants, a long history, and stroking our long white beards for days to think about it.

I should like to go over a group of slides illustrating what I choose to term accessible cancer. Cancer of the skin is obviously accessible, and occurs in the area of the body most commonly exposed—the face. Here is a lady (slide) who illustrates the most common problem of skin cancer in that it is multiple. We know clinically that once a patient has had cancer of the skin, such a patient, if he lives long enough, is going to develop another one, and they are very frequently multiple. Now, this lady has at least five separate lesions that occur in the typical senile atrophic skin with senile keratosis. This lady had been treated for some months with injections of B complex without a biopsy, so this tumor was allowed to go ahead and destroy both thicknesses of the nose in this area. A biopsy of all these showed squamous cell carcinoma. These, we thought, would be simply keratoses, but in the base they had invasive cancer. These were all treated with radiation. A photograph post-radiation (slide) shows that when cancer replaces tissue in toto, and it is destroyed, it leaves a hole, and this has to be repaired; this is almost through the buccal mucosa, but not entirely, and it healed. She has remained well for many years and contrary to my suggestions, she has not so far developed any new carcinomas.

Here (slide) is an early basal cell carcinoma of the lower eyelid. In a characteristic location, it has typical raised borders and central ulceration. There is no problem here in the diagnosis at all. A drop of procaine, a No. 11 Bard-Parker blade, and your diagnosis is made if there is any question about it. We have a rule that we don't radiate patients without a positive diagnosis if it is obtainable, so we even biopsy such lesions. Here is another (slide), even earlier, with typical rose-gray translucency of the tissue which is characteristic of the basal cell carcinoma, again in a typical location. Biopsy makes the diagnosis, and that is all we need to do as far as diagnosis is concerned. Our first reaction on that should be cancer, biopsy, and then treatment.

If you leave such a tumor alone—let it grow to see if it is going to turn into a cancer—this (slide) is what you will eventually have from such a lesion, eye destroyed or the tissues invaded, and face extensively involved. That is the natural history of these tumors, and we must diagnose them clinically in the preceding stage before they do such destruction. This (slide) is a basal cell of some 12-14 years duration treated repeatedly over a period of years with inadequate doses of radiation and now with the eye gone, frontal sinus exposed. This man was dead some months after this photograph was taken; I show it not as a diagnostic problem but simply to illustrate the reason for diagnosing these early.

Another typical location is on the ear. This (slide) is a characteristic squamous cell carcinoma arising usually from keratoses which develop from exposure

to sun, wind, frost bite, etc. There should be no problem about diagnosis, but the legal diagnosis, the 100 per cent diagnosis, is made right there by a little biopsy, which can be done in any office in about two minutes. If you don't make the diagnosis but leave it alone, this (slide) again is the natural history of such a lesion. This poor man had gone for two or three years with a carcinoma of the ear which started out exactly like the preceding one, and now in this stage it was incurable. We tried a quixotic attempt at a radical procedure, but it was perfectly useless in this stage. He died in a few months.

Salivary gland tumors are accessible. They are palpable. I want to impress on you that any palpable mass in the parotid gland must be investigated. Most of them are benign mixed tumors, but these will grow over a period of many years and they can undergo malignant transformation. But one in five —20 per cent of masses in the parotid—are primary carcinomas, and the patient's only chance to preserve the facial nerve is to remove that benign tumor early, before it damages the facial nerve. The treatment is surgical and not radiation, as was done in an attempt to eliminate this tumor (slide). This man has complete facial paresis from the carcinoma of the parotid, although it isn't easily apparent.

Carcinoma of the lip certainly qualifies as an accessible cancer. This (slide) is an exceedingly early case, simply a plaque, hardly even ulcerated—just a persistent change in the mucosa with a little thickening and a little beginning ulcer. Now, a "cold sore" that persists over a period of weeks should be biopsied.

Carcinoma of the lip is not common in the female, but it does happen, and an ulcerating, persisting lesion on the lip should be subjected to biopsy because it is apt to be cancer of the lip.

The multicentric origin applies even to lip cancer. This (slide) is a low grade, well differentiated squamous cell cancer of several years duration which has not had any treatment whatsoever. It amazes me what some of the human race will tolerate. This lesion (slide) definitely started in two areas. Now we don't realize the multicentric origin of cancer too often because the early foci of growth coalesce to form the single tumor that we see clinically; yet it is apparent here that there is a division and on the history he had two separate ulcers—two foci of origin which coalesced to form the large tumor that we see clinically. In my mind, this is past the point of radiation management of lip cancer. To most of us, the indications for radiation or surgery are the opposite to what we frequently think. We see early small lesions on persons who come into the office, and we say, "That is simple; we'll take it off with a local." That is perfectly true and that lesion can equally well be treated with radiation. Somebody comes in like this (slide), and we stop to think of the commissures involved, and feel that surgery would require a rather brutal excision and plastic repair. Our tendency is to say, "Well, let's see what radiation will do." That is an error. These are obligate surgical problems—the large, extensive, low grade exophytic squamous cell carcinomas of the lip.

This prepossessing individual (slide) shows again what the human race will tolerate. This is a carcinoma of the entire lower lip, requiring extremely radical excision, and radiation will not do it in a high enough percentage of cases to make it worth while to try. And if you have tried heavy irradiation and it fails, as it usually will in this type of case, then the problem of surgery is greatly compounded—the problem of plastic reconstruction, swinging of skin flaps and trying to skin graft, and the pulling up of two pedicles is an exceedingly difficult situation with irradiated tissues.

Early lip cancer, or even moderately advanced lip cancer, is curable in a high percentage of cases. We should run around 85 to 90 per cent cures in early cases; the over all salvage is probably 70 to 75 per cent. This man (slide), only about 43 years of age, appeared in the clinic some years ago in the latter part of January, and he said he had a little fissure on his lips for a few weeks before the preceding Christmas, only six to eight weeks duration of which he knew, and it looks like a relatively early lesion; and yet that cancer involves an extensive area. When you examine it and palpate it, you actually can see it. It is a grade three to four lesion and he has bilateral, fixed cervical node metastases. He was dead within a few months. There is not much we can do for this type of patient.

This oral cancer (slide) certainly is accessible, and only requires looking for it and having the patient open his mouth. It is a typical buccal mucosal type of lesion, a low grade, probably a verrucous type of carcinoma such as Ackerman has described. It is a squamous cell as about 90 per cent of the tumors in the mouth are. It arises in a leukoplakic area which you can see, and there is ulceration posteriorly. Now there is no problem in the diagnosis of that at all, and even though the man has a positive Wassermann test don't let that red herring keep you from doing a biopsy. Always biopsy such a lesion and you will have a diagnosis in 100 per cent of the cases with minimal effort on the part of anyone.

Here (slide) is one of the tertiary syphilitic lesions, atrophic glossitis with leukoplakia. Carcinoma of the tongue is associated in about 30 per cent of patients with tertiary lues. Leukoplakia in itself is not harmful, and some leukoplakias are

simply a reaction to irritation such as a callus in the skin, and when the irritating factor is removed (smoking, jagged tooth, bridge work or something like that), the leukoplakia will clear up. Persistent, irreversible leukoplakia, however, is dangerous, and particularly whenever there is any atypia microscopically on a biopsy it should be destroyed. We see individuals with leukoplakia all through the oral cavity, tongue, buccal mucosa, palate, floor of the mouth, and gingiva, and it is simply impossible to cauterize the whole mouth. These patients must be watched rather closely throughout their lives, doing everything we can to stop them from smoking and that sort of thing and encouraging high vitamin intake. When the leukoplakia begins to change in any given area, biopsy it, and if it is cancer, then treat it at that point.

Here (slide) is a luetic glossitis with leukoplakia, with a quarter sized carcinoma arising right here. This is certainly accessible. Biopsy and diagnosis is a simple maneuver, and treatment is relatively simple; radiation to that can be given just as it can to skin cancer. There is also the problem of multiple origins, such as this man (slide) who eventually developed cancers all through his tongue and was simply uncontrollable. In patients with lues, we tend to use surgery rather than radiation in tongue cancer. The cure rate in carcinoma of the tongue is exceedingly bad by either radiation or surgery.

Now here (slide) is a typical carcinoma of the tongue, on the lateral border, in about the middle third—a raised plaque-like lesion ulcerated in the center. These aren't painful in the beginning and the patient doesn't realize what is going on. Of course that subtle problem—lack of pain—is one of the main difficulties of early diagnosis of carcinoma, even in areas such as the mouth which is an exceedingly sensitive spot in the body. The lesion is hard to palpation and its outline can be delineated rather easily by palpation. Biopsy diagnosis certainly is simple, and is obligatory.

Again (slide), this is a case of atrophic glossitis, leukoplakia and a peculiar form of infiltrative carcinoma that you see in luetic tongues, with little surface infiltration or surface ulceration, and wide muscular infiltration throughout a wide area in the tongue. Again, biopsy is the way of diagnosis.

A floor of the mouth lesion is accessible, and biopsy is simple. If you biopsy in the tumor itself, you don't need any anesthetic; there are no nerves in the tumor. If you take some normal tissue, you will need a little topical pontocaine and perhaps a little procaine infiltration, but the biopsy in the center of the tumor needs no anesthetic whatsoever, and is perfectly adequate for diagnosis.

These buccal mucosal lesions, if untreated, go right straight out through the cheek, destroy the whole side of the face, metastasize as you see here (slide), and are of course 100 per cent fatal.

The problem of diagnosis of tumors in the neck is a common clinical one which is seen frequently. In approaching the diagnosis of a lump in the neck, we should start with three premises: (1) exclusive of goiter, most persistent tumors in the neck, in the adult, are malignant; (2) most malignant tumors in the neck are metastatic; (3) most metastatic malignant tumors in the neck come from the head and neck area.

It is perfectly true that almost any malignant tumor in the body can metastasize to the cervical area, but the great majority come from the head and neck, mainly intra-oral and pharyngeal or laryngeal. The first thing we do with a lump in the neck is to examine it by palpation and visual inspection and then examine the head and neck area. I think every physician should be capable of doing a rapid and adequate examination in the oral cavity, and at least visualization of the larynx as a routine part of the practice of medicine. The second step is examination of the head and neck area including the skin, sinuses, mouth, lips, etc. After that comes the general physical examination, if we haven't found the primary, and after that a chest film, blood count, etc. Then and only then we may pick up the knife, but the first approach to tumor in the neck is not incision to see what it is.

Here is a man (slide) with a mass in the neck who had been treated for Hodgkin's disease on a clinical diagnosis, receiving radiation. Nobody looked in his mouth, but he had a huge squamous cell carcinoma of the tonsil that you could smell for 25 feet when he did open his mouth.

There (slide) is a persistent mass in the neck, for which, after going through all the maneuvers I have outlined, I could find no cause. This is a bronchial cleft cyst, entirely a benign lesion. The usual history is that they have been seen, and the mass incised. The first physician encountered the typical creamy material of the cyst, said he thought he had an abscess, and it drained. The wound healed, and the cyst promptly filled up again. The second physician opened it, again drained it, found the so-called pus, took a culture which was negative, and thought, "Ah, tuberculosis." So he treated the patient with x-ray and streptomycin. Eventually, when the cyst filled up again, the next person to look at it either aspirated it or examined the material and found that it had cholestrin crystals and shadow cells of squamous cells and he had a branchial cleft cyst which had been radiated, incised, secondarily infected, and could be an exceedingly difficult problem to remove, whereas in this state, in the virgin

cyst, it is a simple operation, requiring only removal of the entire cyst wall.

Not all tumors in the neck are metastatic, of course. We could find no cause for this (slide) obvious carcinoma. Biopsy showed a rather undifferentiated lesion, thought to be an adenocarcinoma, and it was finally decided it must be a primary carcinoma of the maxillary salivary gland, which it was. The jaw bone was infiltrated, and there were metastases in the neck aside from this primary mass. A radical neck dissection with excision of the mandible on that side has resulted in a cure of some five or six years now. Even with ulceration to that extent, you can salvage these individuals occasionally. But if you don't, the natural history of these neck masses is this. This old gentleman (slide) had a carcinoma of the posterior tongue with cervical node metastases and this is just about to break down. This is perfectly hopeless, untreatable by any method that I know of today. He is a palliative, terminal care problem.

Malignant melanoma is a problem in diagnosis. It is a problem in therapy too, but we must be on the alert in this type of lesion. Here (slide) is a persistent subungual ulceration with destruction of the nail. We must think, not of fungus disease, but of malignant melanoma (melanotic whitlow), even though it is non-pigmented. (As most of them are, actually, in the subungual area in my experience.) Biopsy here will give us the diagnosis, if there is any question about it, and I think that in such a lesion it is far better to biopsy this than to amputate the finger and find out that he did have a fungus infection. However, this is malignant melanoma.

You find most melanomas in the extremities of the body, the feet, hands, or in the head and neck area. They occur anywhere in the surface, of course, but the majority in the distal areas of the body, using the zyphoid process as a central location. Now this (slide) shows the pigmented and non-pigmented melanoma. The diagnosis is perfectly obvious, and there should be no question about it.

Here again (slide), is a persistent ulcer starting from a little black spot on the under surface of the toe. This man had been treated for athlete's foot. He had every sort of ointment that I have ever heard of and had been treated for a period of six months; he had hot baths, hot soaks, everything for this thing, but nobody took a biopsy. Nobody realized that this might be a melanoma, whereas it should be our first thought. This, of course, was melanoma, and although a radical amputation was done, the man had disseminated melanomatosis in a few months, and expired from this tiny primary lesion.

There are two features of these diagnoses of malignant melanoma for which we must watch. One is that when a mole that has been present begins to change, with almost any change except disappearance, we should be suspicious of melanoma. The trap to avoid in making a diagnosis is that of removing the mole "just semi-widely" because you are suspicious of malignant melanoma. Don't do that; if it is benign, then you have done unnecessary destruction, and if it is malignant, you haven't done enough. If it comes back malignant you are apt to say, "Well, we went a little wider than usual, we will wait and see." You are required to sign a death certificate shortly thereafter. If a mole is suspicious, remove it as you would a benign mole, and don't throw it in the wastebasket, but have it sectioned. If it is benign you have done enough, but if it is malignant, then really do a job that is adequate for a melanoma.

The second point to keep in mind is the occurrence of a mole in an adult where none previously existed. This (slide) is such an example in a 45-year-old man. Two years before he developed this pigmented area. Gradually this corona of brown, non-raised pigmentation appeared about it. You can make a clinical diagnosis of malignant melanoma on that. When a slate grey or pigmented area surrounds a mole, or when it begins to infiltrate the skin around it where it isn't palpable, and it is not raised, look out; that is a malignant melanoma. This was treated by wide excision and grafting and he is all right so far for five years.

This (slide) is an example of what I mean. Here is a nevus that had been present since birth in a man of about 50. It began to change, developed a little serous exudate from the surface, and here is the corona of the grey to greyish brown pigmentation about it. That is characteristic and makes a clinical diagnosis of malignant melanoma for you. This was treated by excision and dissection in continuity. Situated close to the axilla, there were only a few cells in the periphery of one lymph node, and so far he has been well about six years. I think Dr. Pack is in the audience, and this is his operation, by the way. He devised it, and it is one of the few advances in the treatment of malignant melanoma in recent years of which I know.

About once a year I get burned on the diagnosis of basal cell, and since we always biopsy them, about once a year I find that a "basal cell" is a non-pigmented melanoma and the difference is, believe me, important.

Breast cancer is certainly accessible cancer; I am sure Dr. Sugarbaker has covered this subject for you, but if you will indulge me, I will point out a few things. This accessible cancer is on the surface,

and some of the diagnostic points are visual, though the important one of course is simply the palpation of a lump. Here (slide) we see the shortening of the breast compared with the other, with a suggestion of spontaneous skin dimpling, and there is some flattening in the lateral contour. Those are all signs of carcinoma. The skin dimpling is perhaps the most important. If it is not apparent with the breast dependent or with the arms raised, if we move the breast about the tumor or move the tumor within the breast, we frequently will produce the skin dimpling. Now that is one of the most important signs of mammary cancer. It is moderately advanced cancer, but nevertheless it is one of our best aids.

If the tumor is allowed to progress, of course, spontaneous dimpling and even retraction will occur. There is no question but that fat necrosis will do it, of course, but even though with fat necrosis you can make a pretty clear clinical diagnosis, you do have to biopsy to be sure you are not dealing with a carcinoma. When you can make a clinical diagnosis of mammary cancer, you are dealing with advanced mammary cancer. It is the solitary, small mass which is clinically non-diagnostic; that is the lesion to biopsy in order to find an early and curable mammary cancer.

Again, here (slide) are spontaneous retraction, flattening of the lateral contour, shortening of the breast and axillary metastases. You don't need to biopsy this. You can make a clinical diagnosis and do a straight radical mastectomy, but the best chance for cure is long gone, and the percentage salvage rate on such a situation is not what we would like to see in breast cancer.

Other mammary cancers, rather than causing retraction due to fibrosis, will produce a bulky tumor which will infiltrate into the skin, and they will, of course, ulcerate right through the skin, as we all know.

Here (slide) is an uncommon form of mammary cancer, but the worst type there is—the so-called inflammatory mammary cancer. We may find only a faint blush of the skin which resembles an erysipelas. Usually in the early stages such as this, it isn't palpable even like an erysipeloid reaction or true erysipelas is, and not infrequently we cannot find the tumor in the breast. In the advanced stages, of course, we eventually will. This type of cancer is almost incurable, even in this early stage. There is something about the potential of this cell that makes it spread widely in the lymphatics. Surgery is practically useless when we find this type of mammary cancer, but even here it might not cause much suspicion at all unless you were well aware of the problem.

Carcinoma of the hands is not as common as on the face, by any means, but again it is the most exposed part of the body and it is the second most common site of skin cancer. Basal cell carcinoma rarely occurs about the hands. It does, but it is exceedingly rare, and most of these are squamous cell carcinomas or epidermoid carcinoma. I use the two terms synonymously. There is no problem about the diagnosis; the biopsy of the edge here is a simple maneuver, and you know exactly what you are dealing with. That should be our first reaction always in such a lesion with the history that it has been there some weeks.

Here (slide) are multiple carcinomas of the hand in a case of long standing chronic arsenic poisoning. This condition will produce widespread skin carcinoma and is an exceedingly difficult problem to treat; it is an irreversible cellular change apparently, and produces multiple carcinomas over the body, particularly about the hands first. You can see the keratoses which are typical. If we leave these alone long enough, and don't biopsy them, diagnose them, and treat them, their natural history is this sort of situation. This man had a few little axillary metastases, and a fore-quarter amputation was done some three or four years ago. So far he is still all right, but you cannot temporize with these lesions.

Carcinoma of the plantar surface of the foot is exceedingly rare. I should think that malignant melanoma of the plantar surface would be more common, but here is a squamous cell carcinoma of the plantar surface. Again it is certainly accessible, it is on the surface, and biopsy will make the diagnosis.

Soft part sarcomas are palpable in the beginning, and will become visible if left alone long enough. There should be no problem in diagnosis, and yet here (slide) are the scars of three previous excisions in which the surgeon apparently did not take the pathologist seriously enough. Now there is the inevitable recurrence and bone fixation requiring an amputation. This was a neurogenic sarcoma in an old gentleman 80 years of age. He did not die of his tumor; he lived about three years but the cancer did not kill him.

There are other lesions which are also accessible cancer, but time will not permit discussing them all now. Included in such tumors would be lesions of the cervix, vulva, penis, anus, rectum, prostate.

So, I would like to summarize by trying to emphasize that diagnosis of accessible cancer actually should not be a difficult procedure; all we have to do is think of it in a given situation, and where it is accessible, biopsy it.

Tumors of the Spine and Spinal Cord—With a Discussion of the Diagnostic Significance of Back Pain*

Eldridge H. Campbell, Jr., M.D., and Robert D. Whitfield, M.D.**

Albany, N. Y.

Introduction

In the great category of patients whose diagnoses have been too long unsuspected or even missed entirely, it is probable that those whose earliest symptoms were common everyday complaints probably lead the list. All too familiar examples are the slight cough of early bronchogenic carcinoma, the mild indigestion of some cancers of the stomach and the equally slight constipation of some malignancies of the large gut. Just as weight loss and evidences of lumenal obstruction are usually late manifestations, so indeed are the weakness and numbness of the extremities in tumors of the spine and spinal cord. Hindsight, which is so much clearer than foresight, and of great value to the physician even if not to the individual patient, frequently reveals that our error lay in a failure to appreciate the significance of a pain in the back. The early diagnosis of neoplasms of the spine and spinal cord, therefore, often devolves about the question of backache.

Osler once remarked that headache might be caused by anything from a high hat to an adherent clitoris; it might with equal propriety be stated that backache may be due to anything from Pott's disease to a pot gut. It would be appropriate at this time, therefore, to consider the mechanism of some pains in, or at least beginning in, the back.

Neural Pathways Involved in Back Pain

It is pertinent at this point to consider the nerves which mediate and/or refer backache. One or more sensory roots may be compressed by a tumor or by a particle of displaced bone. In such an instance the pain is likely to be located not only over the lesion but to be referred to any or all points along the distribution of the involved nerves. Thus, compression of the eighth or ninth right dorsal nerves may result in pains felt principally about the right upper quadrant, one of the many situations where their significance may understandably be missed. Should both the right or left nerves over one dorsal segment be involved, the pain may circle the body as a belt and be described as a "girdle" pain.

A much more widespread but no less severe type of pain may result from inflammation. The products of infection or the sterile meningitis produced by blood in the subarachnoid space irritate sensory rootlets, resulting not only in the well known pain in neck and back but quite frequently in its radiation into the shoulders and hips.

A feature common to pain of intraspinal origin, whether due to pressure or to inflammation, is increase by sudden elevation of intraspinal venous pressure. Thus, coughing, sneezing, compressing the jugular veins or lifting will often precipitate or increase such pain.

Nerve Supply of the Vertebrae and Their Ligaments

The fact that a bone can be sawn or a ligament cut without producing pain proves neither that they have no nerve supply nor that they cannot give origin to pain. It is simply a question of the type of stimulus applied. The gut is a pertinent example: it may be cut or burned with little or no discomfort to the conscious patient, but let it be distended or its mesentery tugged upon and the story is different. Neoplasm, infection, arthritis, and certain types of disk disorders result in pain which is very real and of great diagnostic significance. One should remember that this pain may be brought about either by involvement of the intrinsic nerve supply of these structures or by mechanical compression of adjacent sensory nerves.

The innervation of posterior longitudinal ligament and annulus fibrosis has been worked out in some detail by Roofe, an anatomist who suffered from a ruptured intervertebral disk, as a token of gratitude to his surgeon. It was known that the spinal dura received a sensory branch which left the nerve distal to the posterior primary division, returning through the same intervertebral foramen. Roofe discovered numerous unmyelinated fibres of similar origin which were distributed both to the posterior longitudinal ligaments and to the annulus fibrosis of the two subjacent vertebrae. No end organs were found and it was believed that these were pain fibres. While on anatomical and clinical grounds there is reason to believe the anterior longitudinal ligament and the articular facet joint capsules are similarly innervated, there is yet little experimental confirmation.

A very clever method of demonstrating the origin of referred pain was employed by Sir Thomas Lewis and his pupil, Kellgren. By injecting a few small drops of a strongly hypertonic saline solution into the interspinous ligaments about the spinal column under radiographic control, they believed they demonstrated reference into the corresponding dermatomes.

* Figure 1 published originally in Archives of Surgery and the remainder in the New York State Journal of Medicine.

** From the Department of Surgery, Albany Medical College.

Relation of Spinal Nerves to Vertebral Structures

Where the spinal nerves emerge through the intervertebral foramina they are covered with a tough sleeve of dura and provided with ample room for all physiological needs. Since nature abhors a vacuum, this space is filled largely with fat and huge extradural veins, both readily compressible. The intervertebral foramina may be narrowed in various ways: by pus and granulation tissues as in Pott's disease, by benign tumors such as neurofibromas or meningiomas, by vertebral tumors such as giant cell "sarcomas" or metastatic malignancies which both expand and destroy bone, and by certain malignancies such as carcinomas and lymphomas which are deposited extradurally and form constricting collars about both dura and emerging nerves.

Distribution of Pain in Spinal Nerve Compression

The vertebral periosteum undoubtedly contains pain fibres, as can be demonstrated by the prick of a long needle or the disposition of a few drops of hypertonic saline upon it. Lewis and Kellgren believed that pain of such origin would be felt locally if the involved periosteum were superficial but segmentally if deep. In the majority of instances, however, pain experienced along a dermatome will be found due to nerve root compression. Should the pain be associated with paresthesias in the same area, one can, in our experience, be pretty confident of direct nerve involvement. Such a combination is of localizing value comparable to a light on the telephone operator's switchboard: the origin of the call may be uncertain but the party line on which it comes in is obvious!

Primary Tumors of Spinal Cord

Tumors of the spinal cord may be conveniently divided into two general groups, the intramedullary, which arise from the cord itself, and the extramedullary which, as the name implies, grow from adjacent tissues and neural structures as their size increases.

Intramedullary Tumors. Whereas in the brain gliomas are far more common than dural tumors, the reverse is happily true in the cord. Quite a few gliomas, such as ependymomas and astrocytomas, may be relatively benign, and if discovered in time, can be successfully removed. As distinct from many other spinal canal neoplasms, these lesions produce little pain, save when their posterior extension involves the dorsal rootlets. As the result of interference with the long conduction pathways, however, disorders of strength, sensation, coordination and sphincter control are manifested early. While yet relatively small there may be no block on lumbar puncture, and in the customary absence of x-ray changes it is readily understandable how these lesions may be confused with multiple sclerosis, combined system disease, syphilis and the Guillain-Barre type of multiple neuritis.

At this point it may be of interest to call attention to the fact that whereas the significance of the failure of a lumbar spinal fluid pressure to rise following jugular compression is well known, its corollary, the absence or delay of fall in pressure after jugular release, is sometimes overlooked. Such an oversight is most unfortunate since it is definitely abnormal and signifies a subtotal or incomplete block. The spinal fluid protein is almost always elevated in the presence of a tumor; multiple sclerosis and combined system disease seldom raise protein greatly, although the Guillain-Barre disorder does so conspicuously.

Extramedullary Tumors. There are few, if any, lesions the prospect of which so gladdens the heart of the neurosurgeon as the extramedullary tumors. Since many are benign and very slow-growing, much may be expected toward recovery of useful function following their removal. Meningiomas and, particularly in the lumbar region, neurofibromas, are quite common. Owing to the fact that they increase very slowly in size, the adjacent neural tissue may be compressed or thinned quite out of proportion to the degree of functional loss. Thus it is not unusual to find the cervical cord compressed a third, or even a half, by a meningioma with surprisingly little loss of use of arms or legs. Because of the fact that early sensory losses are usually distal, the clinical localization of the lesion is often several segments too low. Backache and root pains, sometimes girdle pains, may result from root compression. Girdle pains, when present, are of great value in determining the level of the lesion. If there be a reasonable suspicion of a spinal cord tumor a myelogram should be performed. It is one's duty to consider any such neoplasm benign (and hence curable) until demonstrated otherwise.

Malignant Tumors

Until someone invents a counterpart to the Geiger counter which will register mitoses, the first signals of many cancers will arise from their metastases. Malignancies of the lung, the greater curvature of the stomach, the body of the pancreas, and the prostate are all too familiar examples of these long silent primary tumors, whose first clinical signs are metastases. Certain new growths, particularly those of the breast, thyroid, kidney, and prostate, have great proclivities for bone. Hodgkin's disease often involves bone, more especially the spine.

Mechanism of Metastasis. Aside from direct extension from contiguous primary or secondary malignancies, tumor emboli must reach the interior of bone by the bloodstream or by the lymphatics. The name of von Recklinghausen is attached to the

hematogenous theory, while that of Handley is associated with the lymphatic. The implication of the lymphatic channels came as the result of a study of breast carcinoma in which it was claimed that bony involvement resulted from extension from adjacent fascia. A later and very elaborate study of similar material by the great Australian tumor pathologist, Rupert Willis, failed utterly to substantiate these claims. Actually it has never been possible clearly to demonstrate lymphatic vessels in adult bone.

In 1927 the senior author studied periosteal lymphatics in a variety of animals, including man. Many typical channels were demonstrated in the periosteum, particularly in the very young. The richest network was found near the epiphysis in growing bone and it was only at this point that lymphatics were ever found beneath periosteum (Figure 1).

Since metastases show no predilection for the epiphysis, and since it is highly unlikely that lymphatics are present in adult bone at all, some other explanation must be found. In our opinion, the hematogenous theory of von Recklinghausen, as broadened by the venous tidal concept of Batson, most nearly explains the mystery. According to this idea, for which there is much corroborative evidence, tumor emboli having gained entrance into local veins, as is so often observed, may reach bone not only via lungs and arteries, but by local gravitational and tidal backwash may pass in retrograde fashion from terminal branches of systemic veins draining the region of the primary tumor into small branches of the vertebral system of veins with which they connect. From here the emboli pass directly into the huge vertebral and extradural venous network. The channels are there and readily explain the oft-observed tendency of certain carcinomas, such as those of the prostate and breast, to fetch up early and extensively in subjacent portions of the spine or pelvis. A cranial or cerebral metastasis may thus bypass the lung.

Pathology of Metastases. Individual tumors, and even individual metastases, vary considerably in their effects on adjacent bone. Areas of erosion may appear in the x-ray as clear cut, punched out, ragged, or moth eaten, with or without condensation or proliferation of bone. Occasionally increases in bone density are obvious and little or no rarefaction is visible. Pathologic fracture occurs in vertebrae as it does in long bones but less often displays a tendency to heal. Either the vertebral body or the neural arch may be involved; the intervertebral disk is

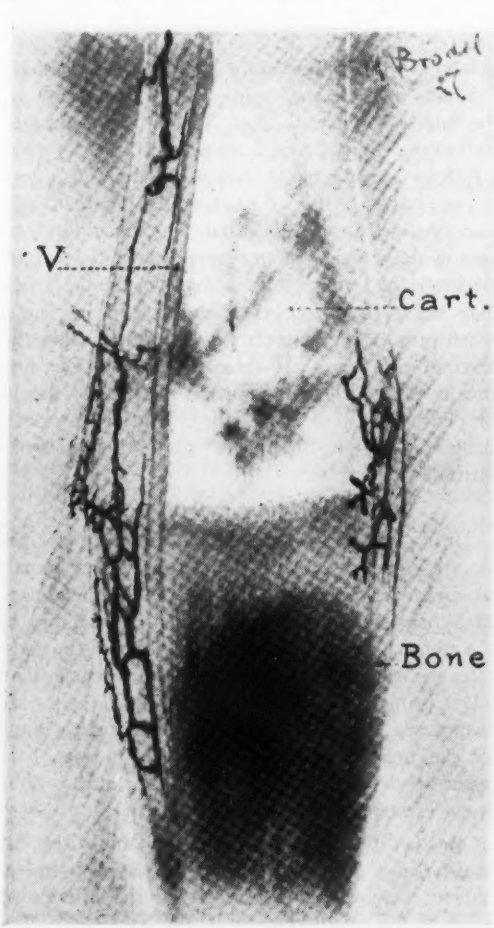

Figure 1. Lymphatics of periosteum at costo-chondral junction.

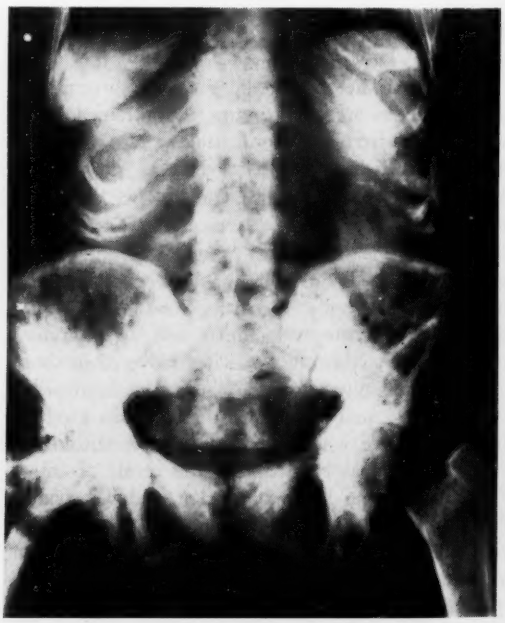

Figure 2. Multiple myeloma, showing "punched-out" areas of rarefaction in pelvis and spine.

singularly resistant to malignant disease, a good point to remember in differential diagnosis. Incidentally, there are few disorders more horribly painful than is nerve root involvement in some pathological vertebral fractures.

A noteworthy feature of spinal metastases is very often an extradural plaque or even collar of tumor, surrounding the cord and/or roots, and thus producing symptoms both by direct pressure and by interference with blood supply. Often there is adjacent bony involvement. While this feature is common in carcinomas, it is also observed in lymphosarcoma.

At this point it may be of interest to call attention to the fact that certain tumors have strong tendencies to metastasize to bone. This likelihood, as judged by autopsy material, is: prostatic cancer (50 to 70 per cent), breast cancer (45 to 55 per cent), thyroid cancer (28 to 34 per cent) and hypernephroma (40 to 50 per cent) (Willis, p. 323). Unhappily, we have all had patients whose very first symptoms were due to a skeletal metastasis. In our hospital the greatest offender in this regard has been the primary lung cancer. Gastro-intestinal malignancies are not quite such common offenders, nor are those of the body of the uterus. Patients who survive two or more years after unsuccessful treatment of carcinoma of the cervix very often develop metastases or extension into the lumbosacral plexus and into the lower lumbar spine.

Hodgkin's disease often affects the spine quite early. At autopsy, Jackson and Parker found bones involved, either by tiny tubercle-like foci, by large destructive lesions, or by intermediate forms in 15 to 30 per cent of all cases. The spine is by all odds the commonest site involved. Of great diagnostic importance is the fact that symptoms referable purely to bony involvement often antedated all others by two to 14 months. Thus backache is not infrequently the earliest and most outstanding symptom. Bone changes as noted in the roentgenogram vary greatly. There may be: first, no demonstrable change, but the presence of metastases may be confirmed at autopsy; second, they may be multiple and osteolytic, with some occasional new bone formation at the margins of the invading tumor; third, the bone trabeculae surrounding small nests of metastatic cells may hypertrophy, resulting in very marked new bone formation, thus giving rise to a picture of markedly increased bone density. Root pains are very common, and if the lesion occurs in the lower lumbar spine and is unaccompanied by x-ray changes, a mistaken diagnosis of tumor or ruptured disk is all too easily made. The authors fell into this very error just recently!

Another fatal disorder which may begin with backache is *multiple myeloma.* Here changes as noted in the roentgenogram are usually demonstrable quite early, at least as related to the onset of pain. While Bence-Jones protein is always sought for in suspicious cases, it is well to remember that its presence is neither constant nor pathognomonic, and usually is found later in the disease. The globulin of the blood proteins is often relatively high.

Paget's disease may be associated with backache. Roentgenographic changes in the pelvis are often demonstrable even before those in the spine or

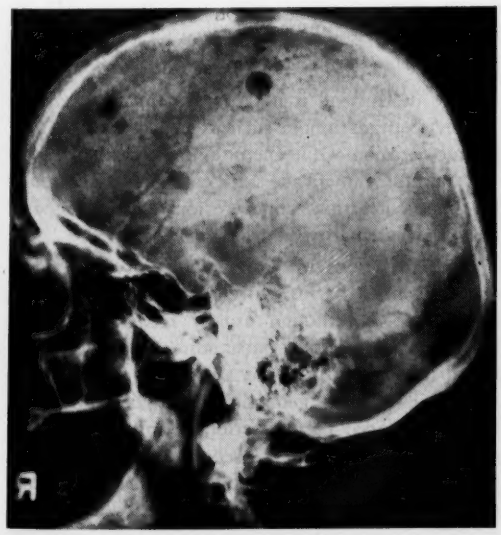

Figure 3. Multiple myeloma, showing "punched-out" areas of rarefaction in skull.

Figure 4. X-ray of dorsal spine showing osteogenic sarcoma secondary to Paget's disease.

skull. Malignant degeneration is by no means uncommon in this disease, the authors having had three cases of sarcoma of the spine arising during its course (Figure 4).

Benign Tumors of the Spine

While the majority of neoplasms of the vertebrae are malignant, one not infrequently encounters benign growths. Since the outlook is so utterly different in the two groups, one should seek proof beyond reasonable doubt before relegating any solitary lesion to the scrap heap of "hopeless cancer." By so doing one will salvage the occasional patient whose roentgenographic diagnosis of malignancy had seemed obvious. The following case is in point.

A 41-year-old man entered the Albany Hospital, September 1, 1939, because of excruciating pain in the back with radiation into the left groin. Coughing, bending, and lifting increased the pain. Abnormal physical findings were limited to marked spasm of the sacrospinalis muscles, thorocolumbar scoliosis with convexity to the left, and a narrow band of hyperaesthesia corresponding to the left 11th dorsal nerve. X-ray films disclosed a destructive lesion involving the body of the 11th dorsal vertebrae and the adjacent portion of the left 11th rib (Figure 5). Operation, performed solely in hope of relieving pain by decompression and rhizotomy, revealed what was believed to be an "inoperable malignancy." Following operation he was given three courses of irradiation with a total of 5100 R. units. Much to our mutual surprise and satisfaction he has remained well these past 11 years and is now working regularly. Pathological diagnoses have ranged from hypernephroma to giant cell sarcoma, with the majority, however, favoring some form of hemangioma.

Figure 5. X-ray following treatment showing recalcification of body of 11th dorsal vertebra and 11th rib.

The moral, however, is that in the instance of solitary lesions one should not give up until metastasis is definitely established.

Giant cell tumors cause both bone destruction and new bone formation; they usually involve the body which, as in the long bones, they tend to expand. Biopsy is usually required for confirmatory diagnosis. They are seldom so situated as to be conveniently curetted with any degree of thoroughness. If the spinal canal is compromised some decompression is necessary. Fortunately their response to irradiation is usually satisfactory.

In recent years the *osteoid osteoma,* another remarkably interesting benign lesion, has come to be recognized. The very considerable pain associated with them is relieved at once by their removal. In the x-ray the relatively small, localized, area of bone density surrounding a much smaller area of rarefaction suggests the diagnosis. Scoliosis, point tenderness and muscle spasm, in the absence of signs of infection, afford further suggestive evidence.

Hemangiomas of the vertebrae are not uncommon, particularly in the lower lumbar region. Some are undoubtedly asymptomatic, others result in mild backache, while a few produce severe back and root pains. The roentgenogram characteristically discloses striated lines of bone density with little or no intervening rarefaction. Decompression of the spinal canal may become necessary if neurologic symptoms appear; spinal fusion is then in order, not only for splinting, but for support.

Differential Diagnosis

Bone destruction is not the private monopoly of cancer. Benign tumors such as neurofibromas may produce erosion while meningiomas, particularly in the cranium, can invade adjacent bone with resulting bone formation, bone erosion, and enormously increased vascularity.

Bone infections of various types are not infrequently confused with malignancy. Of these, *tuberculosis,* which although usually recognizable, has, in our experience, been outstanding. It is widely believed that Pott's disease is a disorder of childhood, and while that in general is true, and while the almost universal pasteurization of milk has greatly reduced the incidence, we see several patients each year whose tuberculous spondylitis has been mistaken for malignant disease. This is particularly confusing when the familiar disk destruction is not advanced, when weakness and numbness of the

lower extremities are present and when paravertebral abscess is not apparent. While this is a most undesirable affliction it is nonetheless a far happier diagnosis to have to render than is cancer!

Staphylococcal and typhoid osteomyelitis, both well known entities to the physician of previous generations, are rarities today.

The ruptured intervertebral disk should not be confused with malignant disease, but may readily be confused with tumor of the spinal cord, or more frequently, of the cauda equina. Trauma by no means always ushers in the symptoms of backache and root pain; in certain cases the herniation may be so large as to compress the cord or cauda equina, resulting in paraplegia and sphincter disturbances. Most massive ruptures occur in the lower lumbar region, where a narrowed disk in the x-ray may suggest the diagnosis. If there be any doubt whatsoever concerning the nature or location of such a lesion, myelography is indicated.

Marie-Strumpfel's arthritis may result in low back pain and muscle spasm long before roentgenographic changes are readily apparent. Pains not infrequently radiate down into the hips and mistaken diagnoses of tumor or ruptured disk are all too often entertained. It is well to remember that obliterative changes about the lumbosacral joints are usually discernible well before the more striking calcifications in the interspinous ligaments.

Other lesions not uncommonly resulting in back pain are: osteoarthritis (associated with generalized disk degeneration), osteoporosis (which may be accompanied by compression fracture), and such malignancies as retroperitoneal sarcoma, lymphosarcoma and leukemia.

Thus the differential diagnosis of backache is often an exercise which will test the mettle of the keenest of clinicians.

Summary

Tumors of the spine and spinal cord are not uncommon; their diagnosis is often delayed by the commonness and customary benignancy of their most frequent presenting symptom, namely backache. While posture, sprains, and occupation, together with some form of arthritis, doubtless account for the majority of such pains, it is of great importance to recall that back pain is the cardinal symptom in most intrinsic disorders of the spine; it is equally important to remember that it may be an early complaint in certain chest and abdominal diseases.

To paraphrase a teaching of the late Dr. Tom Brown:* The back is a mirror in which may be reflected the pain of a great variety of disorders.

*"The stomach is a mirror in which may be reflected the symptoms of disease of almost every organ of the body."

The General Pathology of Endocrine Tumors

Howard T. Karsner, M. D.

Washington, D. C.

This is a summary consideration of tumors of endocrine glands, not so much from the point of view of individual tumors but of the properties of the tumors which are more or less common to all.

The usual approach to the study of tumors is by way of embryology. Most of the endocrine tumors have the cellular pattern of epithelial neoplasms but that does not mean they are necessarily derived from ectodermal or entodermal structures. The cells of the pituitary, the thyroid, pancreas and adrenal medulla are of epithelial origin, but as to other glands there is some question as to ultimate derivation and the situation may be complicated by points of origin near that of other structures. Embryonal displacements or inclusions may thus cause confusion in determining exact origin.

One example is the granulosa-cell tumor of the ovary, a tumor which may induce precocity, disturb menstruation or cause pseudo-rejuvenation after the menopause. It is unlikely that it is derived from mature granulosa; there is question as to what cells of the primitive ovary can give rise to it. Another is the so-called interstitial cell tumor of the testis, an occasional cause of precocity in boys. Adrenal cortical rests occur near the testis and adrenal cortical tumors bring about virilization of females and precocity in boys. Thus, adrenal cortical cells and interstitial cells can produce similar manifestations. To name the tumors as interstitial cell tumors is not yet definitely supported by assays of steroids in the urine. And it may be that some are interstitial cell and other adrenal cortical cell tumors. The controversies as to these and several other endocrine tumors cannot be decided by microscopic features alone.

It is generally agreed that two principal factors are concerned in the origin of tumors, namely, intrinsic and extrinsic or realization factors. In man and other animals there must be an intrinsic factor which predisposes cells to neoplasia, and in some in-

stances this can be identified as hereditary or constitutional, but this factor has not been demonstrated with human endocrine tumors. However, largely because of experimental work and partly because of observations on man, it is certain that the realization factor can be due to absence of, excess of, or imbalance of hormones. In mice, irradiation had led to production of ovarian tumors, but there is no conclusive evidence of similar action in man.

The supporting tissues, blood vessels, fat, etc. of endocrine glands may give origin to tumors of these organs, but our study is directed toward those tumors derived from the special constituent cells. The benign tumors are generally referred to as adenomas, but in only a few types, for example thyroid tumors, are there acinic structures. As indicated above, this terminology is not fully justified on embryological grounds, but the cells in most of the tumors look like epithelium. Curiously, many of the malignant tumors are named carcinomas rather than adenocarcinomas. However, one tumor of epithelial origin in the adrenal medulla is called pheochromocytoma, and certain ovarian tumors are given names because of the appearance of the cells, such as granulosa-cell tumor, thecoma and hypernephroid tumor.

Endocrine tumors may be invasive and metastasize, but the diagnosis of malignant character is often difficult. For most tumors the pathologist diagnoses a tumor as malignant by such features as alterations of pattern and polarity, pleomorphism of cells and abnormalities of mitosis, but these features may not be diagnostic with endocrine tumors for clearly benign tumors may display them. In certain thyroid tumors invasion of blood vessels is the criterion, and in cases of parathyroid tumors invasion of lymphatics is the diagnostic feature. In most others, such as adrenal tumors, invasion into and through the capsule is the principal sign. Metastasis varies greatly. Tumors of the pituitary rarely, if ever, metastasize. Thyroid carcinomas, neuroblastomas of the adrenal and chorio-carcinoma of the testis metastasize widely. The malignant granulosa-cell tumor of the ovary metastasizes infrequently and usually only locally.

Recurrence after removal may be easily identified, as for example in the thyroid. Yet what appears to be recurrence after removal of an adrenal cortical tumor may really be a new tumor derived from aberrant foci of adrenal cortex. Recurrence of granulosa-cell tumors is reported to be as high as 38 per cent, but there is serious question as to whether the second tumor is a new one derived from primitive cells in the immediate neighborhood.

Malignant tumors are said to be occult if the first manifestation is a metastatic lesion, but this is rarely true of endocrine tumors except for that group of adrenal tumors included in the category of neuroblastoma when metastasis to head or liver or bone is observed before there is any indication whatever of the original tumor. The so-called lateral aberrant thyroid adenoma is often the first sign of a thyroid carcinoma. Testicular tumors, especially the choriocarcinoma, may metastasize without clinical evidence of the primary tumor. An exceedingly rare case in my experience was that of a granulosa-cell tumor of the ovary which was first indicated by a pulmonary metastasis.

Many tumors of endocrines are smooth and generally spherical because their situation is such that the form is not altered by the confinement of surrounding structures. However, their form may correspond somewhat to that of the gland if they are entirely within it. Nodularity is not often evident, except in certain thyroid and ovarian tumors, among the latter being the testicular tubular adenoma and an occasional granulosa-cell tumor. Tumors of endocrines are often widely vascularized as is true of the original gland, but this is not regularly correlated with metastasis. It can account for hemorrhage and necrosis.

Certain tinctorial properties of the neoplastic cells are associated with function, as for example the acidophilic adenoma of the pituitary with acromegaly and the basophilic adenoma with Cushing's disease. Peculiar is the fact that there are but few beta cells in functioning islet cell tumors of the pancreas. The assumption is that the cells are primitive and have not yet acquired cytoplasmic granules, but are capable of producing insulin. Many attempts have been made to identify the cells in adrenal cortical tumors which determine whether it is virilizing or feminizing but, in my opinion, the results are not conclusive. Not strictly tinctorial is the Crooke change in functioning basophilic tumors of the pituitary in which the nuclei are hyalinized.

Undoubtedly, the exhibition of function by endocrine tumors is the result of production of hormones. The hormonal effects may be identified by their clinical and physiologic features and in some instances the hormones can be assayed in the urine, the blood and the tumor. The functioning islet cell tumor of the pancreas produces hypoglycemia by means of an excess of insulin. The pheochromocytoma of the adrenal leads to spasmodic or continuous hypertension by its elaboration of epinephrine rich in norepinephrine (arterenol). This is established by assay of the tumors and is attested by

the effects of adrenolytic substances such as the benzodioxanes.

The assay of steroids in the urine is of importance in understanding the action of tumors, but cognizance must be taken of the facts (a) that the steroids in the urine may be degradation products of original steroids and (b) that the state of the receptors may be significant. A presumptive example of the latter is the statement that acidophilic adenoma of the pituitary leads to gigantism if it originates in early life and to acromegaly if originating later. The same assumption is offered as an explanation of unilateral gynecomastia, i.e., that in the one breast receptors are susceptible to the action of circulating estrogens.

Virilization is a clinical phenomenon which may be brought about by different endocrine tumors. It may be manifest as secondary sexual precocity in boys and secondary sexual inversion in females. The precocity in boys may be associated with adrenal cortical tumors or that tumor of the testis usually called interstitial cell. Stature, bone age, mental age, hirsutism, genitalia, voice, etc., are of proportions well in advance of the chronological age. When female children are virilized, adrenal cortical tumors are likely to be responsible. The adrenogenital syndrome of young girls includes broad shoulders, narrow hips, hirsutism of male type and large clitoris. Girls may go on to normal menarche and later become virilized, usually because of a similar tumor. However, in later life virilization may be due to adrenal cortical tumors or to tumors of the ovary, e. g., the arrhenoblastoma, or after the menopause the hypernephroid tumor of the ovary.

The term feminization may mean sexual precocity in girls, so-called rejuvenation in post-menstrual life and certain somatic changes in males. Little girls may be tall, but more impressive is development of breasts, broad hips, large mons veneris and clitoris, female escutcheon and scanty irregularly periodic uterine bleeding, almost certainly anovulatory. The chief neoplasm is granulosa-cell tumor of the ovary, but it may be cortical adrenal tumor, a pituitary tumor, or certain non-tumorous lesions of the hypothalamic region. Most important is the fact that precocity occurs much more often without than with tumor.

Several years after the menopause, a woman may have periodic or continuous uterine bleeding. Since the ovary is atrophic, the bleeding is anovulatory and there are no other manifestations of return of sexual life. Thus, this is not a true rejuvenation. Excluding other causes of bleeding, the lesion is usually a granulosa-cell tumor of the ovary.

Exceedingly rare and in our experience observed in only one case is the woman who matured physically without either primary or secondary sexual development. Her breasts enlarged at age 30 and she developed periodic uterine bleeding, the result of a choriocarcinoma presumably in an undeveloped ovary. Thus, the tumor in this female was feminizing.

The principal changes observed in so-called feminization in males are bilateral gynecomastia, atrophy of testes and reduction or absence of libido. This is a decrease in maleness rather than feminization. It has been reported in several cases of adrenal cortical tumor in young men and is well-known in connection with choriocarcinoma of the testis, extragenital choriocarcinoma and rarely with other tumors of the testis. When assays are made there are increases in output of estrogens and chorionic gonadotropins. However, these same phenomena are probably more frequent in association with hepatic cirrhosis than with endocrine tumors.

Increased basal metabolic rate is well known in association with certain adenomas and carcinomas of the thyroid, evidently because of excessive production of thyroid hormone. Sugar metabolism is altered in some cases of adenoma and carcinoma of the pancreatic islets, a manifestation of hyper-insulinism. Diabetes accompanies adenoma of the pituitary and cortical tumors of the adrenal and occurs in Cushing's disease. However, the glycosuria observed in the hypertensive crisis of pheochromocytoma is not a true diabetes.

Hyperthyroid states are often accompanied by loss of fat, but this is probably because of increased metabolic rate rather than the direct effects of thyroid hormone. Obesity may be observed in some cases of adrenal cortical and ovarian tumors, but the part played by hormones is uncertain. The "moon face" of Cushing's disease is probably more the effect of edema than of accumulation of fat. The removal of virilizing tumors from young women results in a redistribution of fat so that hips become wide and breasts take on normal fat content; just how hormones act is probably complex and certainly not clear.

Increased output of nitrogenous products in the urine indicates destruction of proteins in hyperthyroid states, but again hormones cannot be held to be entirely responsible. In those disorders of endocrines in which there is diabetes, protein can be utilized in the production of glucose, the phenomenon of gluconeogenesis. This has been used to explain loss of resiliency of the skin, abdominal striae and marble skin of Cushing's disease, as well as muscular weakness and osteoporosis in various states.

Changes of electrolyte metabolism are best illustrated by lesions of the parathyroids, including ade-

noma and carcinoma. Clinical and experimental evidence supports the view that the alterations of calcium and phosphorus metabolism are due to excess of parathormone. Only with great rarity do primary tumors destroy the adrenals so as to lead to the changes in salt metabolism of Addison's disease. The changes of chloride and potassium metabolism in Cushing's disease are not constant.

Growth is promoted by pituitary tumors, especially the acidophilic adenoma. We have observed two instances of cortical adrenal tumor in one of apparently homologous twins, the one with the tumor considerably taller than the one without. Increased rate of growth of children in connection with adrenal cortical tumors and granulosa-cell tumor of the ovary is frequent. Perhaps this is brought about by action of their hormones on the growth hormone of the pituitary, yet there is such an interplay of hormonal effects and of genetic factors that no simple explanation suffices.

It is to be emphasized that with the exception of thyroid tumors the neoplasms of endocrine glands are infrequent and in some instances rare. Similar clinical manifestations may occur in other disorders and differential diagnosis must be based on meticulously careful examination. The further study of the functioning tumors of endocrines will be favored if each physician who encounters one will make or have made careful and consecutive endocrine assays. The subject is presented in greater detail in the author's paper: General Pathology of Tumors of Endocrine Glands, Bulletin of the New York Academy of Medicine, Volume 22, pages 503-519, 1946.

Treatment of Cancers of the Anus and Rectum

George T. Pack, M.D.

New York, New York

Anal Epitheliomas. The management of cancers of the anus is distinctly a different problem than the treatment of carcinomas of the rectum. The majority of anal cancers are squamous cell epidermoid carcinomas. They differ in their origin, their histologic structure, their behavior and in the requisites for curative therapy. I know of no other malignant tumor in which such great disparity exists in the methods of treatment, depending on the stage of the disease, as is true for epitheliomas of the anus. This tumor should be recognized very early by the patient, because of the extremely sensitive part of the anatomy in which it develops. It is incomprehensible that in some patients it is permitted to progress to an advanced stage before proper treatment is instituted.

Radiation Therapy of Anal Cancers. If these anal epitheliomas are found early, are of the papillary type, and not deeply invasive, radiation therapy is a very effective method of treatment. One can apply radiation to the anal canal either by means of radium plaques, or by fractionated doses of low voltage, short distance, or contact x-ray therapy, with light filtration and bevelled tip cone placements. It is not the most pleasant experience in the world to have x-rays or radium applied to such a sensitive region as the anus; and yet the individual cherishes a functional anus, as well he should, and agrees to tolerate the temporary unpleasantness in order to conserve this relatively important organ.

The epithelium of the anal canal does not tolerate irradiation well. The skin may become blistered during irradiation with superficial infection, the formation of fissures and associated spasm of the rectal sphincter, all contributing to a most distressing experience for the patient. I have found that if the epithelioma does not actually invade deeply within the anus, it is proper manually to overdilate the anal canal in order to stretch, and even tear, the sphincter in order to prevent the unpleasant tenesmus. After the irradiation has been completed and the reaction is slow in healing, as often occurs, I have again dilated the anus quite vigorously under sodium pentothal anesthesia and by so doing have been able to induce or permit healing to occur rapidly in this irradiated tissue.

Some surgeons have advocated the routine radical resection of the anus and rectum for these epitheliomas, which of course is my practice in those cases which are not deemed suitable for radiation therapy. As an example of the exercise of judgment under these circumstances the following case report is cited:

A 23-year-old pregnant woman was treated for anal epithelioma in a large institution by a man who now occupies the chair of surgery in that university. A biopsy was reported as epidermoid carcinoma. A therapeutic abortion was done and she was then told that an abdomino-perineal rectal resection was necessary. Dr. James Ewing examined the biopsy at the time the patient consulted him, and was of the opinion that radiation therapy

might be tried. The patient was referred to me and received a very intensive dose of irradiation. The severe radiation reaction took over two months to heal, and was aided by repeated dilations of the rectum. This woman is living and well more than 10 years since her treatment. She has an intact rectum; she has normal bowel movements. She has had two children since that time and has no complaints whatsoever.

I have had other patients with sweat gland carcinomas of the anus which have responded to properly planned irradiation provided the cancers were not too deeply infiltrating.

Surgical Treatment of Anal Epitheliomas. If an epithelioma of the anus does infiltrate deeply, if it is encroaching upon the sphincter as sometimes happens, if it has metastasized which it may do in one or two directions, then radical surgical treatment is indicated. The surgical treatment of epidermoid carcinomas of the anus is even more radical than obtains for the average carcinoma of the rectum. This is because the anal canal is abundantly supplied with lymphatics which drain into the medial superficial inguinal nodes, so that often one finds metastases in inguinal nodes from anal cancers.

Carcinoma of the rectum does not metastasize to the groin ordinarily until it first extends downward to involve the anal canal. Infiltrating carcinomas of the anal canal therefore require groin dissections as well as removal of the anal canal. The scope of such an operation encompasses an abdomino-perineal rectal resection with a pelvic dissection of the iliac and obturator lymph nodes, and at the same operative seance and in continuity with the anorectal specimen the major portion of the vulva, if a female, is removed, plus a bilateral groin dissection. The inguinal and femoral nodes are removed in continuity with the specimen including the intervening lymphatics in the skin and subcutaneous tissues.

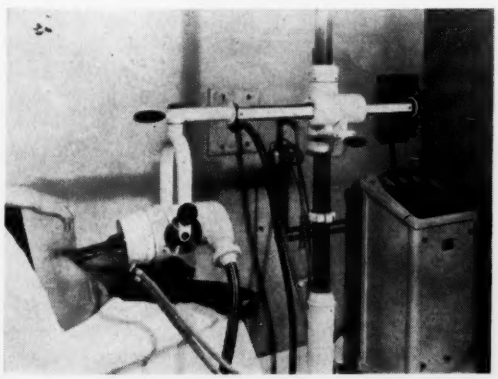

Figure 1. Contact low voltage x-ray therapy of epithelioma of anus using Chaoul apparatus.

If the patient is a male, the same operative technique applies, namely an abdomino-perineal rectal resection with intrapelvic obturator and iliac node dissections, external bilateral groin dissections with a liberal sacrifice of perianal and scrotal skin in continuity. The skin between the anus and groin should be widely excised. All metastasizing cancer cells do not pass unerringly through these lymphatics to the lymph nodes to be filtered out without any of them stopping en route. Whenever separate operations have been attempted, i.e., separate groin dissections, independent of the anorectal resection, recurrence is almost always the rule.

Radiation Therapy of Rectal Cancers. The ownership of a high voltage x-ray machine, the possession of 100 milligrams of radium, or the acquisition of sufficient surgical skill to perform a certain operation do not constitute the indications for preferential selection of one method of treatment for cancer anywhere. This point of view definitely obtains for cancer of the rectum as it is my contention that the therapist should select the method of treatment which in that particular individual seems to be indicated, gives promise of the best results, and is the safest procedure to apply.

Is there ever an indication for the use of x-rays and radium in the treatment of cancer of the rectum? I believe there is. I perform radical abdomino-perineal rectal resections in aged subjects, if they are good operative risks. But if the aged person is a very poor operative risk, if our cardiologists say that this patient will very likely not tolerate the radical operation, then we must suit the treatment to the individual in each case. X-ray and radium treatment of small early cancers of the rectum in aged or infirm patients is highly successful if accurately given, if careful case selection is employed, and if metastases to lymph nodes have fortunately not occurred.

I have used irradiation justifiably as a palliative measure for inoperable rectal cancer hoping to convert it to one that can be technically removed. In defense of this last thesis, we have a large series of cases

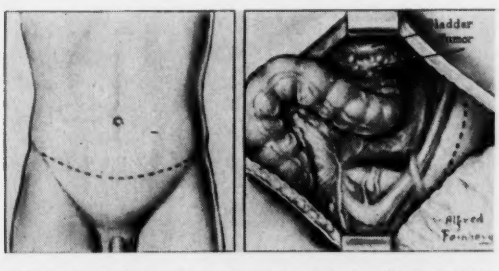

Figure 2. Radical pelvic evisceration. (a) Curvilinear incision. (b) Exposure afforded for pelvic dissection. Dotted line indicates scope of excision of pelvic peritoneum.

in which inoperable rectal cancers have been converted to technically resectable lesions through the intermediation of preliminary irradiation. Dr. Theodore Miller and I presented this subject before the International Congress of Radiology in London. As an example of the practical value of these combined disciplines, I shall mention the case of a patient who came to us with a fixed cancer of the rectum, absolutely impossible to remove surgically; he was treated by irradiation, employing a combination of external supervoltage x-irradiation through a pelvic cycle, plus a perineal port with intermediate voltage, and supplemented by interstitial irradiation. Three months later, the tumor was movable, and an abdomino-perineal rectal resection was performed on this man. He is living and well now some 13 years later.

Another typical example to be cited is that of a young woman who had a laparotomy for an attempt at abdomino-perineal rectal resection by an able surgeon, who abandoned the operation because he found it technically impossible to perform because of its fixity. After a lapse of four months, the cancer obstructed the rectum, and then another surgeon constructed a colostomy; at this time he too made a futile effort to resect the cancer. We later treated the patient by conventional irradiation after the manner that I have described. Two months after completing the program of radiation therapy, it was possible for me to perform the classical abdomino-perineal rectal resection, from which she recovered without complications. We have come to realize that the apparent fixation of some rectal cancers is due not to infiltration by the cancer itself, but to co-existent infection, fibrosis and scarring, which can be greatly improved by irradiation.

The statement that we occasionally treat a primary cancer of the rectum by irradiation without surgery may evoke surprise. I must reiterate, however, that these instances are of course in very selected cases. These cancers are usually papillary, very small, freely movable, apparently confined to the mucosa, without clinical evidence of invasion, not encircling the bowel, not associated with stenosis, occurring usually in elderly subjects who are poor operative risks, and the entire clinical setting is such that after careful study, I have concluded that one can get as good a result by radiation therapy as by radical surgical dissection. In choosing this method as a substitute for radical surgical treatment, we realize that we do not have access to the lymph nodes draining the rectum, and that in some instances, mistakes might very well be made. In reviewing the considerable group of patients in whom this operation has been done, I must say that it has been eminently satisfactory.

Choice of Modalities for Radiation Treatment. One of three methods or a combination of them has proved useful. External irradiation, by treatment around the pelvis with x-ray therapy, the customary pelvic cycle, supplemented either by interstitial radon applications in the form of gold radon seeds in small tumors in the base of the tumor; in some instances preceded by endotherm removal, or in other instances, the insertion of special radium applicators into the rectum with proper filtration for that part of the rectum not to be irradiated, giving treatments daily, or every second day, over a time to the limit of tolerance have been the methods generally employed. We have many elderly people that have been so treated that are living and well for years after treatment of these early cancers of the rectum.

Surgical Treatment of Rectal Cancer. For the average patient we employ, of course, the classical abdomino-perineal rectal resection. As we look back over the history of this operation, and realize that perhaps two surgical generations have elapsed since

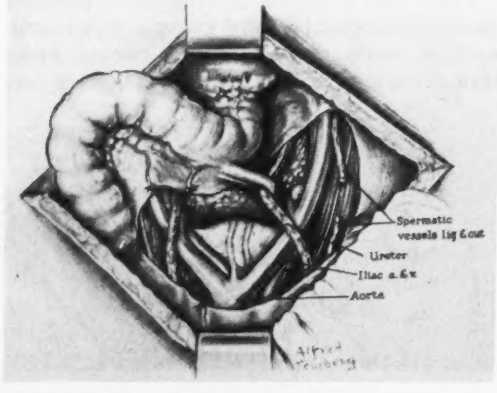

Figure 3. Radical pelvic evisceration. Dissection of peritoneum, fat, areolar tissue and iliac lymph nodes.

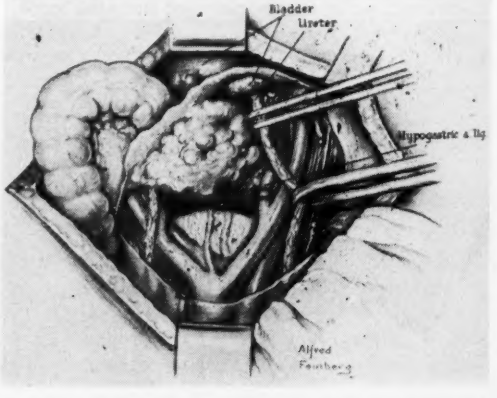

Figure 4. Radical pelvic evisceration. Ligation of hypogastric arteries. Mobilization of ureters.

Sir Ernest Miles described the technique, there has been very little improvement in its performance in these intervening years. One of the reasons why this operation has been so successful is the same reason why radical mastectomy has been approved and has been so consistently practiced throughout the world. The principle in concept is a removal of the entire organ in which the cancer develops, the regional lymph nodes into which one might expect the first relay of metastases to occur, and of equal importance, the intervening lymphatics between the primary cancer and the secondary deposits. The principle has not been applied for cancers in other portions of the body as often as it could be.

Before a cancer anywhere can be treated, it should be diagnosed. Dr. Slaughter has rightly said that cancers of the rectum are accessible, that the majority of them can be felt with the finger, can be seen through the proctoscope, and biopsies of course can be obtained. In this connection we must remember that an individual who has cancer of the rectum may also have cancer of the colon, or may have precancerous polyps higher in the colon. A patient with cancer of the rectum which is not stenotic, should always have a barium enema and roentgen study of the colon with contrast air insufflation. Such x-ray examination is not intended for primary cancer of the rectum which is more directly diagnosed but is indicated, because in our experience there are so many multiple cancers involving the colon and rectum, or polyposis associated with cancer of the rectum.

It is otherwise embarrassing at the time of the planned rectal resection to find co-existent tumors in the large bowel that require more radical surgical treatment. During the past four months, for example, I have performed four total colectomies for multiple cancers of the large bowel, in each instance a one-stage operative procedure being done. In one patient, with rectal involvement, a permanent ileostomy was required, but in the other three, with three, four and five separate cancers, respectively, ileoproctostomy could be achieved with preservation of the sphincter. The short stump of rectum remaining will be constantly available for close and frequent inspection.

Of course I am not prepared to recommend a total colectomy and rectal resection for every person with cancer of the rectum. As a compromise, we must examine the rest of the colon, and hold it suspect all the rest of that individual's life. It is not uncommon after an abdomino-perineal rectal resection to be compelled in future years or during the observational period to resect other cancers of the cecum, or transverse or descending colon. As our backlog of survivals increase, so are we encountering necessities for doing more and more of these multiple operations. One reason, I believe, is that

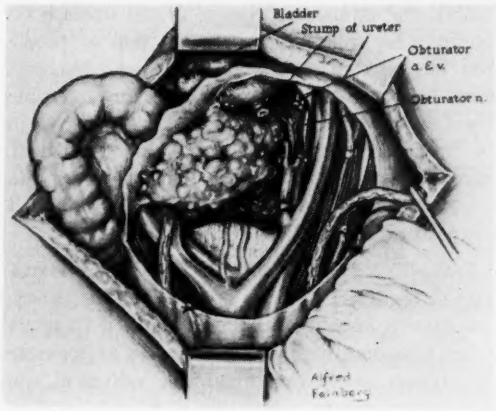

Figure 5. Radical pelvic evisceration. Right ureter transsected. Beginning dissection of right obturator space.

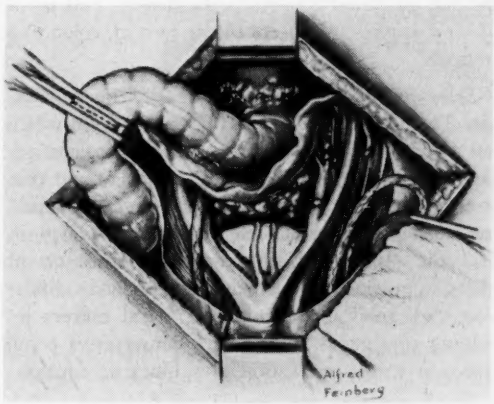

Figure 6. Radical pelvic evisceration. Transsection of pelvic colon.

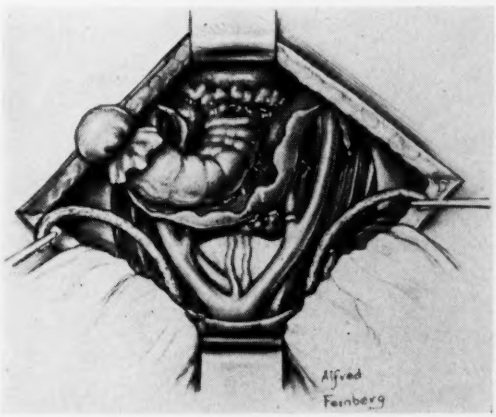

Figure 7. Radical pelvic evisceration. Left ureter transsected. Segment of colon to be excised with rectum.

the precancerous polyp is much more frequent than generally appreciated.

We find only about one in 800 apparently normal people over 40 years of age who have asymptomatic and unsuspected cancer of the stomach on routine x-ray study. But seven per cent of people over 40 years of age, who have sigmoidoscopies done, have one or more polyps in the accessible bowel. Many of these polyps might degenerate in the future and become cancerous. Any individual, then, in whom such a polyp is found, is entitled to a barium enema and roentgen studies to see if polyposis exists elsewhere in the colon.

Palliative Rectal Resection. If a patient has metastases to the liver, only two or three foci, let us say, and without impaired liver function, or if there are nodes extending high along the aorta to convince the surgeon that he cannot cure the individual, and if the rectal cancer is movable, and lends itself to resection with facility, I will unhesitatingly do an abdomino-perineal rectal resection, believing that the best palliation is to resect the cancer. This point of view applies to cancers of the rectum, colon and stomach.

Selection of Surgical Procedures for Rectal Cancer. There are four different operations, from which one may choose the one most suitable for the patient, based on the extent and location of the cancer, viz.; (a) total colectomy and rectal resection for rectal cancers associated with colonic polyposis, (b) the classical abdomino-perineal resection of Miles, supplemented by pelvic lymph node dissection, (c) pelvic evisceration for rectal cancers involving contiguous organs, (d) conservative rectal resection with preservation of sphincteric control.

A. *Rectal Resection and Total Colectomy.* This major operative effort is usually completed in one seance; the multiple staged procedures are never done unless the tumor causes obstruction or is associated with severe infection. The present day availability of blood for transfusions and improvements in anesthesia have enabled the surgeon to complete the operation in a single stage, which represents a great saving in finances and morale.

B. *The Classical Abdomino-Perineal Rectal Resection.* The classical abdomino-perineal rectal resection has maintained its deserved reputation for the past two surgical generations. As originally conceived and executed it was a two dimensional dissection, being quite adequate as far as its upward extent was concerned, and quite adequate below because it included the anus, but it wasn't sufficiently radical in removing the lateral spread of the cancer. Gilchrist and his group in Chicago, by clearing surgical resected specimens, have contributed to our knowledge of the lymphatic spread of rectal cancer and have impressed us with the necessity for an associated dissection of the lateral groups of pelvic lymph nodes. The three-dimensional rectal resection now removes not only the rectum from the hollow of the sacrum, and of course from the base of the bladder, or from the cervix and the vagina, but the lateral dissection includes the lymph nodes in the iliac and obturator groups.

Binkley and Deddish at the Memorial Cancer Center have found that 20 per cent of patients undergoing this operation have metastatic cancer involving these lymph nodes in which the metastases were not clinically detectable at the time of the operation. From their statistics, one might infer that the routine application of pelvic lymph node dissection would offer an opportunity for cure to 20 per cent more people than if the lateral dissection of iliac and obturator nodes had not been done. The upper extent of the operation has also been

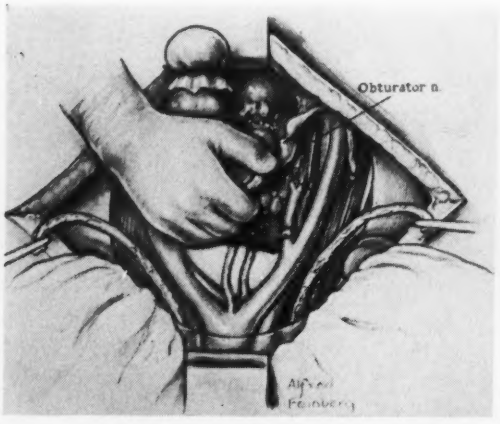

Figure 8. Radical pelvic evisceration. The rectum is dissected free from the hollow of the sacrum.

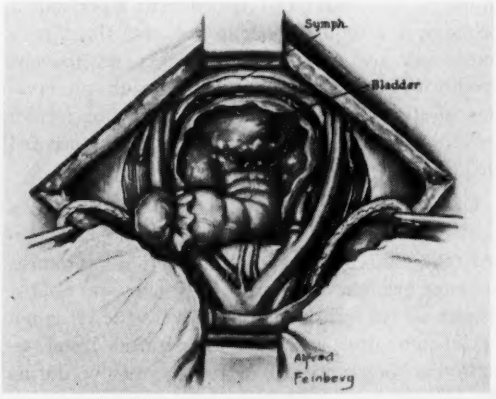

Figure 9. Radical pelvic evisceration. Anterior dissection started in prevesical space.

increased to include the mesentery and lymph nodes as high as the origin of the superior hemorrhoidal vessels.

C. *Removal of Organs Contiguous to the Rectum: Pelvic Evisceration.* Cancers that were formerly considered inoperable because of invasion of neighboring organs, e.g., primary rectal cancers that were adherent to, or invading the urinary blader, uterus, and vagina, possibly associated with the formation of multiple fistulas, are now being resected. It has been found that a considerable number of people who die of cancer of the rectum still have the disease confined within the pelvis. The surgeon no longer hesitates to remove these adjacent organs together with the rectum, such as a part or all of the urinary bladder, the uterus and ovaries, and the vagina. In many women, the uterus, ovaries, tubes and the posterior vaginal wall are removed with these rectal cancers, particularly if there is any anterior extension. More and more surgeons consider it wise to remove the ovaries in all women at the time of operation for cancer of the rectum even though they are not clinically involved; the ovaries have been involved later in a disappointing group of cases.

The extreme limit is the radical operation of pelvic evisceration, in which all the structures of the pelvis are removed. This operation in many cases is admittedly only a palliative procedure. The surgical procedure differs in the sexes only because of the different organs implicated. In the male, the urinary bladder and prostate are removed with the rectum, together with a dissection of all the pelvic lymph nodes. In the female, it involves removal of the rectum, the vagina, the vulva, the internal genitals, the urinary bladder and the urethra.

In pelvic evisceration, one must dispose of the ureters, the terminations of which are removed with the specimen. There is considerable difference of opinion as to the manner of this disposition. Whenever the urinary bladder is removed for pelvic cancers other than rectal in type and the rectum can be preserved, then I routinely practice bilateral ureteral implantations within the colon because the rectum and colon serve as an excellent reservoir for urine. But if a permanent abdominal colostomy is to be done, the decision rests as to whether the ureters should be implanted in the colon, giving the patient a "wet" colostomy, or to implant the ureters in the skin as permanent ureteral neostomies. I prefer the cutaneous ureterostomies for those patients in whom the rectum is removed with the pelvic structures. Patients with "wet" colostomies, i.e., colostomies associated with uretero-colonic anastomoses, in my experience have suffered from an increased morbidity over the ureteral-cutaneous transplants; there is, moreover, a higher surgical mortality; many of these patients furthermore have serious functional renal disturbances later, and some of them die as a result of it.

If the rectum has to be removed in these patients in whom pelvic evisceration is done, I prefer to give them a midline colostomy, which is permanently dry, and which they irrigate every second day, preferably at night. Such colostomies have no constant discharge of feces, no embarrassing bad odor, no retention bag for feces and they are easy to manage. The ureteral skin transplants are readily and safely constructed. With proper catheterization into the renal pelves, these can be kept absolutely dry, and with small urinals on each side these people do not have a bad odor and they live quite satisfactorily.

I have heard physicians say, "I wouldn't be a party to any surgical procedures that would give the patient three abnormal openings, a colostomy and two ureterostomies." I believe that no doctor should

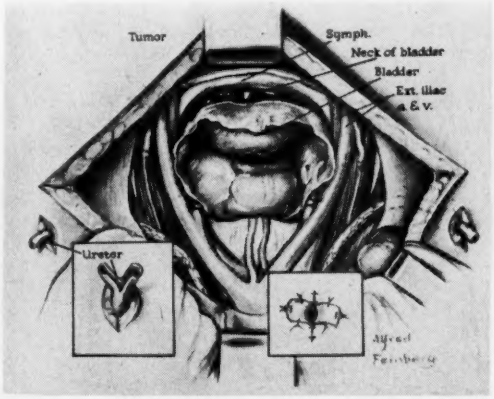

Figure 10. Radical pelvic evisceration. All pelvic viscera dissected free from above. Construction of ureterocutaneous neostomies.

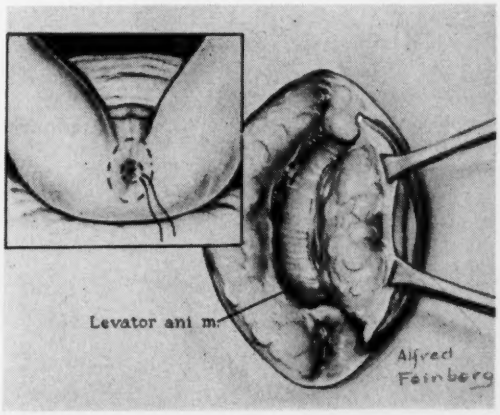

Figure 11. Radical pelvic evisceration. Purse string closure of anus. Onset of perineal dissection.

make these decisions for the patient. If the patient wishes an attempt made to save his life, if he is willing to undergo the inconveniences of the end result of this operation, then it is his decision, not ours, to make. We have no right to suffer our patient's illnesses or disabilities. We may sympathize with them, we might know what we would do in the same circumstance, but we cannot deny them surgical treatment. I believe in this principle of cancer management, namely to give the patient the benefit of the doubt and do everything we can to treat the cancer. After all, their desire to live may be greater than ours under the same circumstances. We shouldn't play God and make this decision for them.

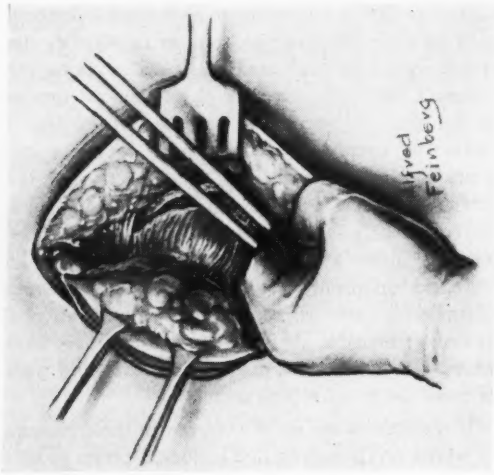

Figure 12. Radical pelvic evisceration. Levator muscles incised to release perineal outlet.

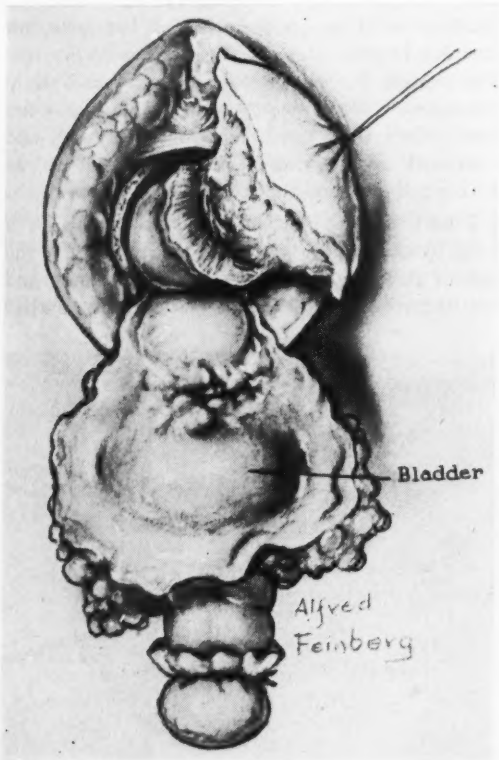

Figure 13. Radical pelvic evisceration. Perineal dissection completed.

Conservative Rectal Resection with Preservation of Sphincteric Control. It is a strange paradox that one who practices pelvic evisceration and believes in it should at the same time advocate the conservative treatment of rectal cancer in selective cases. I am of the opinion that a definite place exists for preservation of the rectal sphincter if one exercises good surgical judgment. The indications assume that the surgeon is familiar with the natural history of the disease and is rigidly selective of the patients deemed suitable for these conservative procedures. In other words, plot the operation for a particular patient. I have done many conservative rectal resections with preservation of the rectal sphincter, and I will continue to do them. If these patients subsequently develop recurrences in the operative field, or in the pelvis, this is proof that bad judgment has been exercised in selecting such cases for this operation. If, on the other hand, they exhibit distant metastases in the liver, that is part of the natural history of the disease; it is an act of God over which we have no control.

Unfortunately, some surgeons who have persistently advocated preservation of the rectal sphincter have attempted to increase the indications for this operation to such an extent that they take out more and more advanced cancers, until ultimately they find their recurrence rate to be so high that they abandon the operation altogether. There is a happy

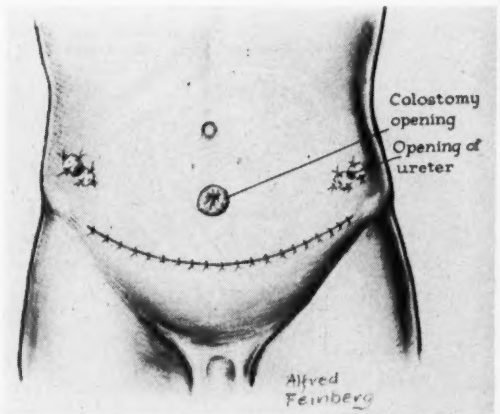

Figure 14. Radical pelvic evisceration. Closed abdominal incision. Location of colostomy and bilateral ureterostomies.

medium. One must avoid trying to fit the patient to an operation of your choice; instead, choose the operation for the situation and extent of the cancer in that particular patient.

Given a patient with rectal cancer, if it is a polypoid type, if it is freely movable, if it is sessile, if it doesn't encircle the bowel, if it is grade II or grade I in anaplasia, if it is papillary in structure, if it is situated well up above the anal sphincter, then one may employ one of several measures by which the tumor can be removed and the rectal sphincter saved.

What are the technical methods by which it can be done? If the cancer is at the level of the recto-sigmoid or slightly above it, above the level of the peritoneal reflexion, and if it is a very early cancer, one can do a superior segmental resection with primary anastomosis through an abdominal approach. In this operation the surgeon performs a dissection of the pelvic lymph nodes, resects the mesentery, removes a liberal segment of the pelvic colon, mobilizes the descending colon, and anastomoses it low from above.

The ease of performance of this operation can be enhanced by the Cherney incision. A transverse incision is made from anterior superior iliac spine to the opposite iliac spine, the recti muscles are severed just above the pubis and the patient is hyperextended on the table so that they are jack-knifed with the fulcrum so to speak over the sacrum. This position increases the antero-posterior axis of the pelvis as it does in the Walcher position in obstetrics. It affords a remarkable exposure of the pelvic structure, so that the recto-sigmoid is so readily accessible that one can construct a low anastomosis, just above the anus. In the end to end anastomosis, interrupted silk sutures are used to comprise two layers throughout for mucosa as well as for the muscular layers. In the female we often drain the site of the anastomosis by a colpotomy stab wound in the vagina. I cannot recall a single instance of a recto-vaginal fistula requiring surgical closure. In the male, the drainage is constructed posteriorly through the perineum. The peritoneal floor is repaired well up above the level of the anastomoses.

Another procedure sometimes employed is a modification of the old "pull-through" operation of Hochenegg. I have used the modifications of this operation that have been described by Doctors Bab-

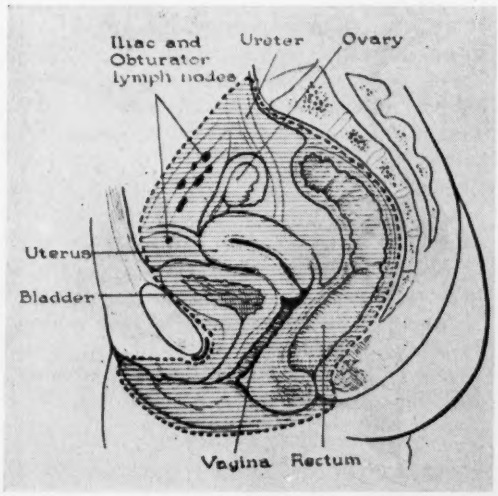

Figure 15. Radical pelvic evisceration. Diagram with shaded region to indicate the extent of dissection and viscera removed.

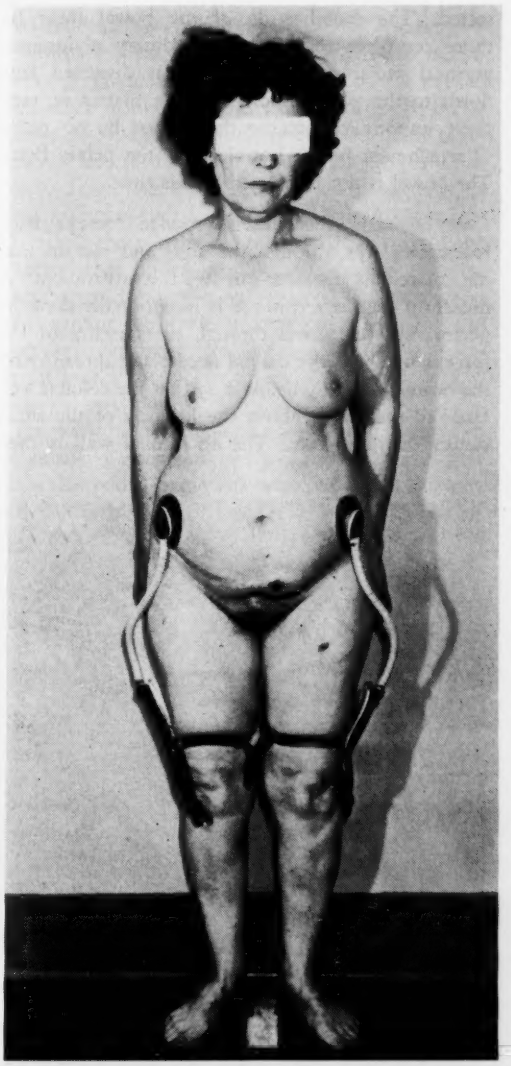

Figure 16. Radical pelvic evisceration. Post-operative state.

cock and Bacon, but my patients have not enjoyed the good continuance of the sphincter that has occurred in their capable hands. I have been using an intussusception technique. The intussusception of the tumor-bearing segment of the rectum or recto-sigmoid cannot be prolapsed readily through the manually dilated but intact sphincter in patients who are fat, or have much fat in the mesentery or surrounding the rectum and the sigmoid colon; but in a thin subject with an early cancer of this type, it is indeed a very satisfactory and easy method of dissection, and one that is rather dramatic to witness.

The operation is started abdominally in a manner similar to an ordinary abdomino-perineal rectal resection. The bowel is mobilized, but not transected. The mobilization of the bowel must be more complete than for the ordinary abdomino-perineal rectal resection, and it is dissected free down to the pelvic floor; this is a matter of very great importance because there must be no point of attachment of the bowel above the pelvic floor. The bowel is not transected at this time.

An assistant then inserts sponge forceps with fenestrated tips, through the anus and rectum into the colon. The operator can feel this instrument. A breach of aseptic technique is intentionally done by perforating the bowel through the fenestra of the forceps with a heavy curved needle and thread tying the bowel and tying below it, so that the colon is well fixed to the clamp above the location of the small cancer in the rectum. The abdominal wall is then closed in layers without drainage and without colostomy.

The patient is then placed in the lithotomy position with the sponge forceps protruding from the anus. The rectum and ligated distal colon are thoroughly cleansed and irrigated. The rectum is manually dilated, antiseptic solutions are used within the lumen, and then the protruding clamp is covered with a sterile rubber glove. The operator merely grasps the clamp and by pulling on it the bowel becomes intussuscepted. It is done without great difficulty if the dissection from above has been complete. As the bowel does prolapse and come out, even the anal canal is intussuscepted, and the tumor is readily visible on the outside surface. With the scalpel, a circular incision is made just above the anus to transect the bowel. The tumor bearing segment of the bowel is withdrawn, and it too is transected well above the site of the cancer. The telescoped cut segments which protrude are then anastomosed, using an outer layer of interrupted silk sutures and an inner layer of interrupted chromocized catgut sutures. The method is similar to the technique sometimes followed for prolapse of the rectum. The anastomosed bowel is easily pushed upward through the temporarily relaxed sphincter, and no external perineal evidence of the operation exists except a stab wound for drainage. These pa-

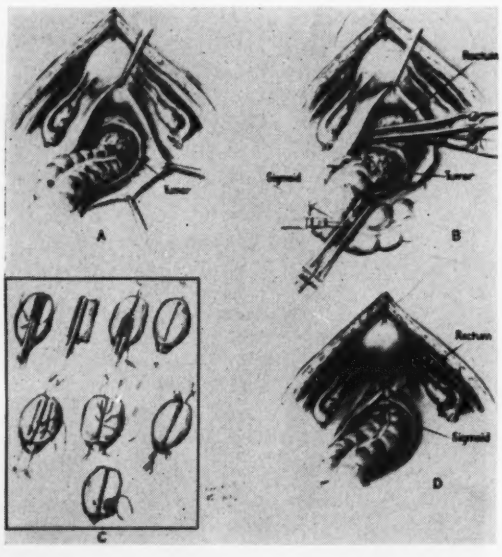

Figure 17. Superior segmental resection of recto-sigmoid with primary anastomosis.

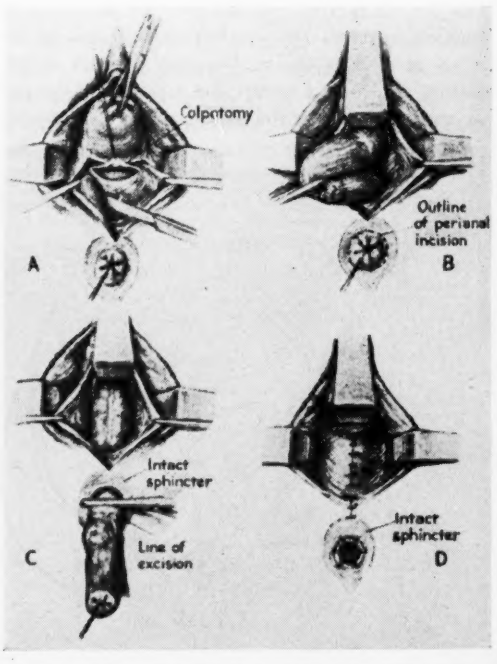

Figure 18. Conservative rectal resection with preservation of sphincter. Burch modification of pull-through technique for females.

tients experience good control of their rectal sphincters.

My only defense for advocating pelvic evisceration on one hand and conservative operation on the other for cancers of the rectum is that one exercise meticulous surgical judgment in the selection of cases.

Bibliography

1. Pack, G. T., and Livingston, E. M. Introduction: The treatment of cancer of the rectum and rectosigmoid. In: Pack, G. T., and Livingston, E. M., Editors: The Treatment of Cancer and Allied Diseases. Paul Hoeber, Inc. 1940, New York, Vol. II, pp. 1454-1471.
2. Pack, G. T., Gallo, J. S., and Wilkinson, B. F. Roentgen therapy by the method of Chaoul. Jour. Med. Soc. New Jersey. 36:16-21, 1939.
3. Pack, G. T., and Gallo, J. S. Indications for conservatism in the surgical treatment of rectal cancer. Jour. Med. Soc. New Jersey. 41:85-90, 1944.

The Relation of Pregnancy to Malignancy

Daniel G. Morton, M.D.

Los Angeles, California

Pregnancy is accompanied by profound changes in the maternal organism, some of which have close relationships with growth phenomena. It is important then for all of us, in our ordinary daily clinical contacts, to be aware of these relationships and to know something of their practical significance. It is unfortunate that much of what is known regarding this subject is not really factual, but is based upon observations of an incomplete nature, some pointing in one direction and some in quite the opposite direction. We must rely, in our judgments, upon as careful an interpretation of the evidence available as is possible, and we must realize that we may be in error and that as new evidence is acquired we may have to change our opinions.

Among the alterations regularly occurring in pregnancy which may have a bearing on growth phenomena are those in hormone concentrations. One of the chief hormonal changes occurring in the gravid state is a marked increase in the titre of circulating estrogen. It has been demonstrated experimentally that it is this increase in estrogen which is responsible for the hypertrophy and hyperplasia of the myometrium and of the smooth muscle coats of neighboring organs, phenomena which are prominent features of pregnancy. More abundant estrogen is also probably responsible for the marked increase in vascularity of these organs and of the breasts. Estrin is responsible, too, for the significant epithelial changes which occur in the uterus and in the breasts in pregnancy. Since estrogens in general, and other closely related chemical compounds have been implicated in the genesis of certain tumors in animals, it is extremely important that we know as much as we can of the possible relationships of these compounds with human tumors, and of any effect which pregnancy might have upon such tumors.

While pregnancy is accompanied by increase in concentration of hormones other than estrogen, such as gonadotrophin and progesterone, there has been no evidence to suggest that they have any particular relationship to growth phenonema of the kind under discussion at this time.

Now, for some of the evidence relative to the effect of pregnancy upon tumors: The observation has been made many times that carcinoma of the breast "grows like wildfire" when it co-exists with pregnancy. How reliable such observations are is difficult to determine, but I think it fair to say that in some instances breast cancer does indeed grow rapidly when the patient is pregnant. It has also been observed that under similar circumstances cervical cancer seems to grow more rapidly. The temptation is to attribute the acceleration of the growth of these neoplasms during pregnancy to the increased estrogen titre, although it is very doubtful if there is a specific relationship.

Emge's work 15 years ago with fibroadenomata of the breast in pregnant rats strongly suggested that the acceleration in growth which was present may have been incident to the increased vascularity of these tissues in pregnancy rather than to any specific growth-promoting property of estrogens. Whatever the cause, pregnancy does seem to be associated with some acceleration of co-existent breast tumors in many instances, in both man and animals. Without at this time documenting my statement, I think it is pretty well accepted that pregnancy and estrogens have no effect directly or indirectly upon tumors arising in organs other than those of the reproductive system including the breasts, tissues upon which estrogens normally exert an effect.

Additional evidence contraverting a carcinogenic rôle for estrogens in humans are the following observations:

1. Estrogens may cause temporary regression in certain cases of advanced cancer of the breast. The use of estrogens as a palliative measure in hopelessly advanced cases of mammary cancer in elderly women has been reported rather frequently in recent years. In only rare instances has acceleration of the growth resulted from the estrogen administration.

2. Allen and associates have administered large doses of estrogens over prolonged periods of time to a considerable number of elderly women without having observed any cancers whatsoever.

Let us examine the evidence on the other side of the argument: It has long been known that estrogens increase the incidence and speed the appearance of mammary cancer in certain susceptible strains of mice. Estrogens do not cause mammary cancer in strains in which cancer does not appear spontaneously, however. While estrogens seem to play an important rôle in the production of these mouse tumors, there are obviously other even more fundamental conditions necessary, e.g. genetic constitution.

Both Gardner and Perry have reported the development of cervical cancers in mice after estrogen dosing, provided the animals were saved from mammary cancer or pyometra which often appeared first. However, massive doses of estrogens given to monkeys and other animals over prolonged periods of time have failed to produce cancer of any kind.

It has not been shown that estrogen effects lead to cancer in the human being, but there are several interesting suggestive relationships. In the histories of individuals developing carcinoma of the endometrium, menorrhagia, late menopause, and hyperplasia of the endometrium, all conditions associated with hyper- or persistent estrinism, appear much more commonly than they do in women without carcinoma of the endometrium. The incidence of carcinoma of the endometrium in cases of granulosa cell tumor of the ovary is four or five times the general incidence. In addition, there have been several cases of carcinoma of the endometrium reported following prolonged estrogen therapy. It is also known that carcinoma of the uterus is relatively rare in women who were castrated before they reached the age at which they would normally cease menstruating. Finally, one of the first observations suggesting that there might be a relationship between ovarian function and the growth of breast cancer was that occasionally large, fungating mammary cancers recede in a remarkable fashion after castration alone.

All of these observations suggest that estrogens exert an effect upon the tissues of the reproductive tract, including the breasts, which makes them more susceptible to the development of cancer. It has not been shown, however, that estrogens ever *cause* cancer in humans, or for that matter that they even exert a *specific* accelerating effect upon the growth of an already existing cancer.

There are a number of practical clinical problems pertaining to the relationship of pregnancy and of estrogens to malignancy which I would like to discuss briefly.

1. Cervical cancer in pregnancy. Such cancers "seem" to grow more rapidly when the patient is pregnant. In general, the rule should be to treat the cancer at once. Sometimes it will be expedient to terminate the pregnancy operatively before starting treatment, though actually the institution of anticancer therapy will usually result in the spontaneous termination of the pregnancy in a short period of time.

The only exception to this rule of immediate treatment, I believe, should be when the pregnancy has not quite reached the period of viability. In this event it would seem to me to be justifiable to defer cancer therapy until viability has been reached and delivery accomplished by the most appropriate means, provided that the delay does not exceed three to four weeks at most. Since the treatment of cervical cancer inevitably results in castration, we as physicians are not placed in the position of having to decide whether or not continued ovarian function would have a deleterious influence.

Other forms of genital cancer rarely co-exist with pregnancy and therefore need not be discussed.

2. Breast cancer occurring during pregnancy. As discussed above sometimes pregnancy seems to accelerate the growth of breast cancer. Therapeutic abortion or premature termination of a more advanced pregnancy may often be indicated, but it should never be done, in my opinion, with the idea that it will increase the patient's chance of cure. Pregnancy does not make the difference between the existence and the non-existence of cancer. It is possible, of course, that whatever cancer is present or remains after treatment might be influenced to grow a little faster if the patient is pregnant; sometimes this is important, but not always.

If the patient is far along in her pregnancy, six months or more, it is my feeling that termination is rarely indicated. The breast lesion can be treated in the appropriate manner without regard to the pregnancy.

In like manner, the question of preserving ovarian function in a patient with breast cancer may be discussed. Castration will not, I believe, on the basis of established facts, increase the patient's chance of cure. It may have an influence upon the rate of growth of cancer which may still be present. If none is present, then it makes no difference whether the patient has or does not have ovarian function so far as continued existence is concerned. If the patient is young, however, it may make a lot of difference as to how comfortably the patient exists. For these reasons I believe that usually ovarian function should be preserved in young women.

3. Estrogen therapy after treatment for cancer of the genital tract and breast. This is a controversial subject. In line with the arguments already advanced with regard to pregnancy and ovarian function, I believe that it is quite safe to employ small doses of estrogens in women who have been treated for cancer of the reproductive apparatus, when symptoms cannot be controlled in some other manner. This is not a conclusion based merely upon the reasoning given above; it is a conclusion based upon extensive experience. For years we have prescribed estrogens as indicated for women seen in a cancer follow-up clinic without ever having had occasion to regret it. When we give comparatively large doses of estrogens to women with advanced breast cancer and often see regression it seems foolish to withhold the tiny doses necessary to relieve disagreeable menopausal symptoms in patients apparently successfully treated.

Summary

1. Pregnancy, with its increased titre of estrogens, may accelerate the growth of malignant tumors of the reproductive tract and of the breasts.

2. The acceleration associated with pregnancy may not be a specific effect of the estrogens, but may be due to the increased vascularity of these tissues in pregnancy.

3. The termination of pregnancy in individuals with cancer of the reproductive apparatus is often indicated for sound reasons, but in itself will not increase the patient's chance of cure, though it may prolong life.

4. The practical implications of these conclusions are discussed with regard to cervical cancer in pregnancy, breast cancer and pregnancy, ovarian function and cancer of the reproductive apparatus, and the use of estrogens after cancer therapy.

Treatment of Cancer of the Face, Mouth and Neck with Irradiation*

Charles L. Martin, M. D.

Dallas, Texas

Cancer of the face, mouth and neck was selected as a subject because malignant disease involving the exposed cutaneous surfaces and the mouth is unusually common in the southwestern states. A U. S. Public Health survey conducted in 1939 in the Dallas-Fort Worth area showed 33.8 per cent of 3683 cancers recorded to originate in the skin. Dermatologists believe that this high incidence results from constant exposure to sunlight and hot winds which produce multiple precancerous lesions in the thin, high colored skin observed so frequently in the blondes and sandy complexioned people who make up a majority of our white population. The common practice of using chewing tobacco and snuff in the rural districts may account for the high incidence of intraoral cancer.

Treatment

In our clinic the lesions under consideration are treated primarily with some form of irradiation, often augmented by electrosurgery. Some patients are then referred to the plastic surgeon for the repair of defects or the removal of necrotic tissue or of incompletely controlled malignant disease. Although the majority of the cases to be discussed do not require such procedures, it should be stated at the outset that the author believes that the cooperation of a competent head and neck surgeon is essential if the best results are to be obtained. We are also convinced that the efficient combination of the two methods tends to make some of the recently devised radical operations unnecessary.

X-ray Technics

Many efficient technics have appeared in the literature but only those which are used routinely in our clinic will be described in this paper. Epidermoid carcinomas which measure less than two cm in diameter and show little or no infiltration are treated with low voltage roentgen therapy. The treatment factors are: 85 kilovolts, 5 milliamperes, a target skin distance of 16 cm and a filter of 1.0 mm of aluminum. Each small tumor is treated with a transparent cone having a diameter large enough to insure the radiation of an appreciable margin of normal skin. Daily doses of 1200 r (measured in air) are given for four or five days, the total dose being 4800 to 6000 r. The projecting portions of thick lesions are removed by electrosurgery before the roentgen therapy is started. A rather severe reaction appears in about seven days after the treatment is finished and the exposed area may be temporarily denuded. Healing should be complete in six to eight weeks and the scarring produced is minimal. The cosmetic results are good, especially on the lip where the vermilion border is often restored to normal. As with all x-ray technics the

* This is a condensation of the two papers presented at the Third Annual Mid-West Cancer Conference, which were profusely illustrated with lantern slides. This paper was presented first at a meeting of the New England Roentgen Ray Society, Boston, Massachusetts, April 21, 1950.

gum should be protected, particularly when the teeth are present.

Although large neoplasms have been cured with this technic the reactions are severe and healing is slow. When Coutard first described his divided dose technic with higher voltages in this country in 1932 it impressed us as a worth while procedure for large superficial lesions and our modification was described in 1935.[1] At present the treatment factors are: 220 kilovolts, 20 to 25 milliamperes, a target skin distance of 50 cm and filters varying from 0.5 mm of copper and 1.0 mm of aluminum to 0.8 mm of tin, 0.25 mm of copper and 1.0 mm of aluminum. The area treated should include a margin of normal skin about the tumor and the ports vary from 10x10 to 15x15 cm. As a rule a dose of 300 r measured in air is given daily (except Sundays) up to a total of 3600 r. The sequence of events is similar to that observed with the low voltage technic but healing may not be complete for two or three months after the treatment is finished. Here again it is desirable to remove polypoid masses by an electrosurgical procedure before roentgen therapy is started. Many radiologists produce the same carcinolytic effect by administering a much larger total dose over a longer period of time and contend that the normal tissues are spared by increasing the time factor. In the author's opinion this contention has not been proven and more experimental work should be done in an effort to establish the most favorable time factor.

Interstitial Radium Technic

It is our practice to treat all intraoral lesions and many of the larger ones on the face and neck with implanted low intensity radium needles which have been completely described in a recent article.[2] They were first used in our clinic in 1930 and were patterned after needles described by Cade[3] in 1929. With them it is possible to accurately administer carcinolytic doses of gamma rays to tumors of various sizes and shapes and use a relatively long time factor. In the author's opinion this procedure reduces the damage to normal tissues to a minimum and possesses other practical advantages over radon seed implantation described in an article[4] published in 1932.

All of the needles are made of platinum-iridium and have wall thicknesses varying from 0.5 mm to 0.6 mm which are sufficient to filter out all beta rays. The sizes found most practical have over-all lengths of 11.0, 27.0, 51.0 and 61.0 mm, contain 0.66, 1.33, 2.4 and 3.3 mg of radium sulphate and have active lengths of 0.5, 1.5, 4.0 and 5.0 cm, respectively. The radium content per cm of active length varies from 0.66 to 0.88 mg.

When the time of implantation is fixed at seven days, charts may be prepared from Quimby's tables giving the doses in gamma roentgens delivered at various points about the active lengths of the four needles. Paterson and Parker state that most epitheliomata can be destroyed when each part of the tumor receives not less than 6000 gamma roentgens in eight days and that most areas in the mouth will tolerate 12000 gamma roentgens without the formation of necroses. It becomes evident then that satisfactory results should be obtained with needle patterns so arranged that the point doses within the treated area vary from 6000 to 12000 gamma roentgens. Many such patterns have been worked out and in practice it is only necessary to use one or more of them in doing a radium needle implantation. It is true that the implantation of some of the more complicated tumors requires some ingenuity but the problem is not as difficult as it may seem at first glance.

All needles are stitched in place and attached to guy threads which are tied into a tag with identification information printed on it. Patients receiving this form of treatment are placed in the hospital for a week so that they may be observed each day. Under ideal conditions the reaction reaches its peak in about three weeks and has subsided in six weeks. Healing requires periods varying from six weeks to several months, depending on the size of the needled area, and daily boric acid ointment dressings are applied to skin surfaces until healing is complete. Since the technic recommended does not produce uniform dosage, small areas of necrosis may require special care. External applications of alvagel or vitamin A and D ointment may clear up these complications but in some cases electrocoagulation or other surgical procedures are resorted to.

Intraoral areas are cleansed with a good mouth wash and painted daily with five per cent mercurochrome. Superficial patches of necrosis often respond to the application of Scott's solution once or twice daily. When teeth are removed before low intensity needles are used, bone damage is reduced to a minimum but in some cases, particularly those in which large lesions are treated, it may be necessary to remove devitalized bone with rongeurs or electrocoagulation or to excise portions of the mandible. It is the author's opinion that the number of patients developing this complication is smaller than that observed with any other type of intraoral irradiation.

Repetition of Treatment

The radiologist should make an all-out effort to produce a cure with his first series of treatments since the second attempt is never very successful and may actually produce harmful results. If cures

are to be produced the bold application of an efficient technic is preferable to a cautious approach, even though a few untoward sequelae may result. The patient with cancer of the skin who has received relatively small doses of roentgen rays given once a week over long periods of time by the "watch and wait" method constitutes one of our most difficult problems. In these cases the tumor bed has been damaged so that normal tissues may not be able to recover from carcinolytic doses. When recurrent nodules are observed in heavily irradiated areas they should be removed by surgical intervention. The application of large doses of irradiation to such regions will almost invariably produce a slough.

Cancer of the Face and Neck

The technics used in the treatment of cancer of the exposed cutaneous surfaces were described in detail in a recent article.[5] It is the author's opinion that carcinomas on the backs of the hands do better with electrocoagulation or surgical excision but all such lesions originating on the skin of the face or neck may be treated successfully with irradiation. The smaller neoplasms measuring less than 2.0 cm in diameter respond well to the low voltage technic while the large ones are successfully handled with the modified Coutard technic or radium needle implantations. The dosages recommended in the first section of this paper are capable of eradicating both basal cell and squamous cell carcinomas, and a differential diagnosis is not too important. Large squamous cell carcinomas growing on the forehead and in the temples seem to respond best to 200 kilovolt therapy. Interstitial therapy is used for large lesions on other portions of the face and neck, particularly when there is much deep induration present.

Small cancers of the canthi and eyelids are treated with low voltage roentgen therapy. The cosmetic results are good and the eyes should not be damaged when protective shields are properly placed beneath the lids. Cancer of the conjunctiva responds to the same technic. When shielding is carefully done the end results are excellent. Our experience indicates that carcinoma of the inner canthus often receives poor treatment in general practice. Recurrences tend to extend well down into the orbit, over the nose or directly inward so as to enter the nasal passage and the ethnoid sinuses. Such lesions have been successfully treated with low intensity needles inserted vertically into the sides of the orbit or longitudinally over the bridge of the nose. In a series of 27 advanced lesions of this type seen from 1937 to 1948 good primary healing was obtained in 25 (88.8 per cent). Of this group 73 per cent had been treated unsuccessfully elsewhere with caustics, surgery or some type of irradiation. Failures occurred in the patients with deep extension through the bony structures. The five-year salvage amounted to 73.3 per cent. An occlusion of the tear ducts, which often follows irradiation therapy, can be prevented by careful dilatations carried out during the healing stage. A slight conjunctivitis was noted in some of these cases and cataracts observed at the time of treatment became noticeably worse in three. However, these complications seemed preferable to the deformities resulting from radical surgery.

Small cancers on the nose are usually eradicated with fulguration or electrocoagulation. The larger ones respond well to low intensity needles when little or no cartilage is involved. Massive growths which have destroyed much of the nose and extend well down into the nasal passage are handled in a different manner. After the presenting tumor and the involved portion of the nose have been removed with the endotherm knife, x-ray therapy is administered directly into the nasal passage by means of the modified Coutard technic. A round cone covering a port measuring seven cm in diameter is used in most cases. After healing takes place a false nose attached to glasses materially improves the patient's appearance. Plastic surgery may be carried out at a later date but should be delayed for some eight or nine months since large basal cell tumors sometimes recur even when very thorough treatment has been carried out.

Cancer of the Lip

Although good results from irradiation have been reported for years all but the smallest cancers of the lip are still handled with surgical procedures in most tumor clinics. It is our practice to use the low voltage x-ray technic on all such lesions measuring less than 2.0 cm in diameter unless they are accompanied by deep infiltration. The lower lip is turned downwards over a lead foil shield placed on the chin and held in place by a cone of the proper size during each treatment. This procedure protects the gums and teeth. The cosmetic results obtained with this method are superior to those produced by any surgical procedure thus far devised. All other carcinomas in this region, regardless of their size, are implanted with low intensity radium needles. As in other locations fungoid masses are removed as a preliminary procedure. When the corner of the mouth or the inner cheek is involved the pattern can be easily extended to include all of the malignant tissue. A small gauze sponge is kept between the lip and the underlying teeth while the patient is awake and in this way damage

to the alveolar margins is avoided. If the neoplasm has invaded much of the mucosa of the lip the eradication of all tumor tissue leaves a defect which may necessitate a pastic repair operation. However, this is done in a surprisingly small number of the patients treated. In a group of 77 patients with advanced cancer of the lip treated prior to 1944 the five-year salvage amounted to 33.7 per cent. In view of the fact that 45, or 58 per cent, of these cases had metastatic cervical nodes at the time that they were treated the salvage rate is considered worth while. It is also worthy of note that primary healing produced by radium needles alone was satisfactory in 80 per cent of the group. In the remainder residual tumor or sloughs were removed by electrosurgery.

Cancer of the Ear

It is our impression that in general practice a greater percentage of failures occurs in the treatment of cancer of the ear than any other superficial portion of the body. Carcinolytic doses of x-rays applied over the auricle so frequently produce some damage to the cartilage followed by painful reactions that we now treat almost all small cancers in this structure with fulguration or the endotherm knife. Although some deformity may result such an easy method has proved very satisfactory in a busy clinic. Painful necroses observed following the application of large doses of low voltage x-rays to one surface of the ear can often be handled satisfactorily by dissecting out a button of cartilage somewhat larger than the damaged area. Immediate relief of pain is obtained and the resulting defect is not unsightly when the underlying skin surface can be left intact.

The care of cancer of the ear becomes difficult when the whole auricle is involved, when malignant tissue has extended into the auditory canal or the surrounding tissues and when the cervical nodes are invaded. Such cases may be said to be advanced. The following plan of treatment has yielded the best results in our hands. After the involved portion of the auricle has been removed flush with the side of the head with the endotherm knife, the remaining deep seated cartilage is removed by blunt dissection. The residual tumor tissue now lies in a single plane which can easily be implanted with one of the standard radium needle patterns. When the external auditory canal is invaded small 0.66 mg needles are stitched around its periphery. The treatment of metastatic nodes will be covered in another section. Radical surgery carried out in this region must of necessity damage the facial nerve. Since low intensity needles do not affect nerves they provide the method of choice.

A group of 35 advanced cases treated three to seven years ago by this method has been studied. Good healing occurred in 22 (63 per cent) and 18 (51.4 per cent) remained well for three to seven years. Failures occurred in the patients who developed deep bone invasion or distant metastases.

Intraoral Cancer

The surgical management of cancer within the mouth is difficult and even the most radical operators depend to some extent on irradiation therapy. In different centers various combinations of intraoral cone therapy, external roentgen therapy, intraoral radium contact devices or implanted radon seeds are used. In our clinic technics have been developed whereby low intensity radium needles can be used for all intraoral lesions except those situated very high or very low in the pharynx. A rather extensive experience has convinced us that this plan produces the best results with the fewest sequelae.

The selection of the correct pattern in a given case and the proper insertion of the needles sometimes becomes a tedious and time-consuming problem, particularly when the tumor is large and involves several portions of the mouth. However, the restoration of function with a minimum of deformity justifies all of the trouble involved. Patterns which have been used successfully in carcinomas of the inner cheek, floor of the mouth, gums, anterior pillar, soft and hard palate, tonsil and the various portions of the tongue have been published.[2] The more enthusiastic advocates of low intensity radium needles such as Cade[7] and Paterson[8] have not used them in close proximity to bone. We are now engaged in a study of a series of approximately 100 cases with cancer of the gums treated exclusively with this method. Although the study is not yet complete we are impressed with the low incidence of bone necroses requiring secondary surgical procedures and now carry out implantations on the hard palate as well as alongside the alveolar margins without fear of serious sequelae.

Although actual malignant invasion of bone is still looked upon as an indication for radical surgery marked improvement has been observed in some such lesions following the use of low intensity needles and it seems possible that the danger of dissemination of malignant cells at operation may be lessened by such preliminary treatment.

A group of 218 patients with intraoral cancer treated with needle therapy prior to 1946 has been studied carefully. Although many of these cases were far advanced good primary healing was obtained in 139, or 63.7 per cent. More than one-third of the lesions in 93 cases that have remained well for three or more years measured 3.0 cm or more in diameter. The five-year salvage in 171

patients treated prior to 1944 was 40 per cent. When one considers the fact that many of these cases had metastatic nodes, that some were untraced and that others died of intercurrent diseases, a five-year salvage of 40 per cent seems worth while.

Metastatic Cervical Nodes

The complete care of patients with cancer of the head and neck must include the treatment of metastatic cervical nodes. Although block dissection is generally accepted as the treatment of choice it offers little hope of cure except in carefully selected cases. Brown and McDowell[9] have published an analysis of the results obtained in 410 operable cases selected from six of the best surgical centers in this country. The five-year salvage for this entire group was reported as 25 per cent. Since many patients are not suitable for surgery this figure indicates that more than three-fourths of the entire group will eventually be referred for irradiation therapy. A problem of this magnitude justifies an intensive search for better methods of using irradiation.

The author has been able to completely control no metastatic cervical nodes with any form of external irradiation available to him except some of those which are secondary to transitional cell carcinomas in the pharynx. It is our belief that the dose needed to cure epidermoid carcinoma growing in a lymph node is considerably larger than that needed to cure the primary lesion. If this concept be true efficient treatment necessitates the administration of very large doses. In 1929 Quimby and Pack[10] showed that the skin will tolerate very large amounts of irradiation when the total amount is given partially as gamma rays and partially as 200 kilovolt x-rays. In 1931 Quick[11] advocated a combination of radon seeds implanted in a metastatic gland with external x-ray therapy as a curative procedure. In 1940 Martin, Munster and Sugarbaker[12] described the technic in detail.

The weakness in this technic seemed to lie in the small areas covered and in the poor distribution of radon seeds shown in roentgenograms of implanted areas. The substitution of long low intensity radium needles for seeds not only provides a better distribution of gamma rays over a larger field but the heavier filtration which eliminates all beta rays gives a better factor of safety for the normal tissues. In most locations it is possible to insert a planar needle pattern into the lymphatic bed which carries efficient irradiation well beyond the palpable nodes. The first patient receiving this plan of therapy was treated in 1935 and he is alive and well today.

At the present time the procedure is carried out as follows: low intensity radium needles are first inserted through small incisions in the skin of the neck so as to set up a planar pattern designed to deliver doses ranging from 6000 r to 12000 r to the palpable nodes and neighboring lymphatics in a period of seven days. On the day after the needles are placed x-ray therapy is started. The factors are 220 kilovolts, 25 milliamperes, a target skin distance of 50 cm and a filter of 0.4 mm of tin, 0.25 mm of copper and 1.0 mm of aluminum. A dose of 350 r measured in air is administered daily until a total of 2100 r has been given. The portals vary from 10x10 to 10x15 cm. The technic has been described in more detail in published articles.[13, 14, 15]

Since 1937 all head and neck cases entering our clinic with metastatic cervical nodes secondary to epidermoid carcinoma have been treated in this manner and the total number exceeds 300. A series of 146 patients treated prior to March, 1944, was reported at a recent meeting. Of this unselected group 40, or 27.3 per cent, have remained well for five or more years, 91 are known to be dead and 15 are untraced. Although the follow-up studies were not complete we can report that the palpable nodes disappeared in 102, or 70 per cent, of the entire series.

In old age groups five-year statistics do not reflect the true worth of a method of treatment. An analysis of the 91 cases that did not live five years and are known to be dead bears this out. Only 46 of these patients died of the cancer treated, while the remaining 45 succumbed from a variety of other causes.

All of the 146 patients reported had proven primary epidermoid carcinomas but since no block dissections were done, histological proof of the presence of cancer in the enlarged nodes was lacking in most instances. Rapid extension of the disease following the removal of single nodes for diagnosis observed soon after we started the work induced us to discontinue this method of diagnosis. A large experience with head and neck cases has led us to believe that our clincial diagnoses are rarely wrong except when the palpable nodes are very small. The needle biopsy method has been used for several years and the high percentage of positive reports obtained on nodes diagnosed as malignant by clinical observation has strengthened our confidence in the clinical diagnoses made in the reported series.

Since some surgeons still contend that no patient with proven epidermoid carcinoma in cervical lymph nodes has ever been cured by irradiation alone a series of 17 patients with histologically proven nodes treated prior to 1944 was studied. It was found that nine of these patients have survived for periods varying from five to ten years.

Many seen to have the opinion that our rather heroic therapy gives rise to extensive fibrosis and scarring which later produces excruciating pain in the neck. It is true that the overlying skin shows some atrophy and freckling and areas of telangiectasis sometimes appear, particularly in the lower cervical region. When large areas are treated some subcutaneous scarring results and it may produce a moderate degree of stiffness of the neck. However, none of these reactions is painful. A histological study of tissue removed from areas producing pain has almost invariably revealed the presence of uncontrolled cancer.

Summary

Radiological technics are described which may be used with considerable success in the treatment of cancer of the face, mouth and neck without the use of radical surgery. They are economical in that the time needed for their application is relatively short and the equipment required is modest.

Bibliography

1. Martin, J. M., and Martin, C. L. Modified Coutard roentgen therapy. J.A.M.A., 104:605, Feb. 23, 1935.
2. Martin, C. L. Low intensity radium needles. Am. J. Roentgenol., LXII, 467, 1949.
3. Cade, S. Radium Treatment of Cancer. Wm. Wood & Co., New York, 1929.
4. Martin C. L. Small radium needles versus radon implants. Am. J. Roentgenol., 27:240, 1932.
5. Martin, C. L., and Wright, C. Treatment of cancer of the face, mouth and neck with irradiation. J.A.M.A., 134:861, 1947.
6. Martin, C. L., and Martin, James A. Treatment of advanced cancer involving the ear. Am. J. Roentgenol., 40:750, 1948.
7. Cade, S. Malignant Disease and Its Treatment by Radium. Williams & Wilkins Co., Baltimore, 1949.
8. Paterson, S. The Treatment of Malignant Disease by Radium and X-Rays. Williams & Wilkins Co., Baltimore, 1948.
9. Brown, J. B., and McDowell, F. Treatment of metastatic carcinoma of the neck. Annals of Surg., 119:543, 1944.
10. Quimby, E. H., and Pack, G. T. Skin erythema for combination of gamma and roentgen rays. Radiol., 13:306, 1929.
11. Quick, D. Interstitial radiation in metastic cervical nodes of epidermoid carcinoma. Annals of Surg., 93:380, 1931.
12. Martin, H. E., Munster, H., and Sugarbaker, E. D. Cancer of the tongue. Arch. Surg., 41:888, 1940.
13. Martin, C. L. Treatment of metastatic cervical lymph nodes. Am. J. Roentgenol., 41:819, 1939.
14. Martin, C. L. Treatment of metastatic cervical lymph nodes with irradiation. Tr. Sect. Laryng., Otol., & Rhinol., A.M.A., pp. 86-108, 1940.
15. Martin C. L. Treatment of metastatic cervical lymph nodes; new method. Texas State J. Med., 37:236, 1941.

Recent Advances In Cancer Therapy

Danely P. Slaughter, M.D.

Chicago, Illinois

It may seem to many of us that we are not getting very far in the treatment of cancer but I assure you that the picture has changed considerably in the last ten years. I should like to review with you the three fields in which I think there have been some advances made, and indicate some of the tendencies that research is taking. The three fields are: (1) the newest one, that of chemotherapy and its subsidiary, the endocrine approach in the treatment of cancer; (2) the field of radiation; and (3) surgery.

Chemotherapy has only recently played any important part. It is still essentially a research problem. There is no drug today that will cure cancer as far as we know. We have had a lot of disappointing results. We have all been through the teropterin phase which was completely innocuous both to the patient and the cancer, but this opened up the era of the anti-folic acid derivatives, and a number of exceedingly toxic derivatives have been found. One of these, aminopterin, will affect cancer, and cause regression. It has not cured anybody yet, and its most useful field is in bone marrow disease, particularly myelogenous leukemia. The drug is not practical in the treatment of most other tumors however, because it is so exceedingly toxic. I think it is fortunate that the Borgias didn't know about it. There are many other drugs that are being investigated; urethane, stilbamidine—we could go on through the whole list—all of them are essentially still in a research field.

A practical advantage, however, has come from the endocrine research. This was opened up about ten years ago as you all know, by Dr. Huggins, through his demonstration of the reaction of human prostatic cancer to castration or to the administration of estrogens, particularly in the form of stilbestrol. This was the first demonstration of the relation of the human tumor to the endocrine system. We have known about it in animals for a long time; but this opened up the field in human beings. Since then, mammary cancer has become an exceedingly important field of investigation in endocrine relationships. This was started empirically, after the demonstration of the effect of estrogens on prostatic cancer; it occurred to somebody to see what androgens would do in mammary cancer. And then it was found that estrogens would work too in certain cases.

I will summarize for you our feeling about the use of these drugs in advanced mammary cancer. In the first place, I want to make two things clear. These hormones should never be used prophylactically; and they should never be used to treat breast cancer that can be treated effectively by any other means. They are in no sense a substitute for the standard, known curative treatment of cancer. They

do not replace surgery nor do they replace radiation, even as part of the definitive treatment or as palliative treatment. They should be used only in the advanced case of dissemination where treatment by any other means is not practical. There are two reasons for this: (1) These hormones are exceedingly dangerous—they are a double edged sword, and must not be used carelessly. They are dangerous because either estrogen or androgen will, in some instances, speed up the growth of cancer. So far we cannot predict except in a general way in which cases that may happen, so you may make your patient worse. (2) In the hypertensive or latent cardiac these steroids will cause sodium and water retention and particularly the androgens may create an acute cardiac decompensation. In our earlier work on this, we had to hospitalize several of our patients as emergencies before we realized this fact. Androgens are more dangerous in this manner than the estrogens but either can do it. Another thing that we have observed which illustrates that last point is that women following radical mastectomy who have just a latent edema without swelling of the arm—bare compensation in the lymphatic return on that side—may, if they are given androgens, get an acute swelling and massive edema within even a few days. This simply is an illustration of the effect which these steroids can have on sodium and electrolyte balance.

Now we use the androgens in advanced mammary cancer in women whose cancer started before, or during, or shortly after the menopause. The standard dosage is 100 mgm. of testosterone propionate given intramuscularly three times a week. Sometimes we will give this daily for five or six days. If within three to four weeks there is no regression, the drug is not going to be useful. In our series, we have found that in about 40 per cent of these women of this age group, the tumor will react with significant regression. This regression occurs both in soft tissue and in bone. It is temporary, although we have a few patients who have gone on now for three and four years with repeated courses after reactivation.

There are other annoying side effects of the androgens if they are given in a therapeutic dose. These patients will develop acne like an adolescent boy; they develop hirsutism, they have to shave; there is a masculinization, with deepening of the voice; there is an increase in libido and these are changes that are quite definite, and as I say, quite annoying to many women.

With the estrogens, on the other hand, the dosage is quite different. There we use only three to five milligrams a day, by mouth. This is a physiologic dosage and in the postmenopausal woman with an intact uterus, this dosage will cause physiologic stimulation. The endometrium will react with a normal menstrual cycle, symptoms will cease with withdrawal of the drug every month. It also will make fibroids which have been quiescent since the menopause bloom like peonies in May; it will cause cervical erosion. In a patient with cervical stenosis, hematometra has been created; and it will create changes in the opposite breast of these women. There are a lot of physiologic reactions that occur, so remember that these hormones are double edged swords and we must be careful. In my opinion, they must not be used prophylactically, and they must not be used when any other effective method of treatment is indicated and available.

This (slide) illustrates an osteolytic metastasis with collapse of a lumbar vertebra from a mammary cancer. This is in a relatively young woman. She was put on androgens, and this picture is some four months later, showing the recalcification. Now in many of these patients pain will be relieved without roentgen evidence of the recalcification. I can't explain that but it nevertheless is true. These patients also develop an increased blood count, which is part of their sense of well being and euphoria if you will. We didn't realize that for a while. We kept taking blood counts to watch them and finally realized that in practically all of them their counts increased and we felt that would be better. These patients will gain ten to twelve pounds during the first month of treatment and that of course is simply water retention. When you stop the drug, they have a diuresis almost as if they had been given mercupurin.

This (slide) is an illustration of the effect of estrogens. This woman had a large fungating mammary cancer with massive axillary metastases. She refused surgery, which from our point of view was just as well. She was put on stilbestrol and she had no other treatment. Four months after beginning treatment, the lesion had regressed entirely clinically, there was just a slight palpable thickening there and yet biopsy still showed viable cells. You can see the tremendous difference. The estrogen was continued for a few months and discontinued after eight months of treatment and the tumor reactivated and grew up to a fairly large size again, and she again reacted to administration of stilbestrol.

Stilbestrol in the older age groups, over 65, is much more effective than the androgens, and we use it in that age group; and use the androgens in the younger age group. The group that gives us the most difficulty is the ages from about 50 to 65. We find that in general, the androgens are somewhat more effective.

We are running a test, just a vaginal smear, to test for estrogen activity in those postmenopausal women who show evidence of persistent estrogen activity below a level at which the endometrium will react; we use androgens on those even though they may be 55 to 65 years of age.

Now only about 40 per cent of the patients in either age group will react favorably. The most dramatic results we find are with estrogens in the aged group. Most of the reaction will persist for about ten months and then, even if the drug is continued, the tumor will reactivate in the majority of instances. We have had a few who will go on for two or three years, and the tumor will remain quiescent. If we then stop the drug, in eight or nine months the tumor will again reactivate, and will then regress. We don't know how long this will go on.

We have some patients who reacted to testosterone and then become refractory to it; and the tumor then reacted to estrogen. Some of them will become refractory to estrogen and then will again react to testosterone. So it is a confused field about which we do not know very much, and I just want to impress upon you that these are somewhat dangerous drugs to use indiscriminately.

The next area of advances in cancer therapy is in the field of radiation. I think this will have been adequately covered for you by Dr. Lawrence and by Dr. Martin, and so I will not comment except to mention two areas that I think are of interest.

One is the use of the betatron. This is still entirely in an experimental stage, but we have found that in many deep seated, deep lying cancers we can produce regression with this modality that we cannot with conventional x-ray machines. We have found some confusing and surprising things. The exit dose with the use of this instrument is much higher than the entrance dose. The absorption curve is almost the reverse of the usual x-ray machine, and we have unwittingly in the first few cases created severe x-ray burns, severe x-ray dermatitis and even sloughing in the portal of exit with almost no reaction on the point of entrance. The tumors react exactly as they would to conventional x-ray, with the tumor dose expressed in roentgens, but with this instrument we can deliver a much higher dosage to esophageal lesions and other rather deeply lying tumors.

As a surgeon, I must admit that I suspect that this form of treatment may possibly replace surgery in the treatment of at least upper thoracic esophageal lesions. We have exactly the same problems with it however. If you destroy the cancer you get mediastinitis, and a fatality if you destroy cancer that has gone clear through the esophageal wall. So the problem is still an experimental one but we do have a new weapon which will deliver a much greater tumor dose in depth than conventional x-ray machines have done so far.

Now in the field of isotopes, far be it from me after Dr. Lawrence to say even a word. But I would like to discuss one phase of thyroid carcinoma which to me is one of the most fascinating observations in human cancer in years. This fact has also changed our point of view in the surgical treatment of thyroid cancer. It has been demonstrated in a few instances that metastatic thyroid cancer which is rather undifferentiated, which does not pick up radioiodine, can be made to redifferentiate towards the normal, take on a more normal appearing histologic picture, and can be made to pick up radioiodine when all the normal thyroid tissue has been removed. So far, we think this is best done surgically, rather than to destroy the normal thyroid with radio iodine, because we may reach the limit of tolerance dose in attempting to eliminate the normal thyroid tissue. Now that is the first time that we have seen a human cancer redifferentiate towards the normal in a state of physiologic need—in other words in a state of myxedema after the complete normal thyroid has been removed. This can also be enhanced by the use of thyrotropic hormones. This is still in an experimental stage, but it is practical enough now that it has changed our approach to thyroid cancer with disseminated disease, or even without disseminated disease. We feel, at the moment at least, that the treatment of thyroid cancer is still fundamentally surgical, and even though most tumors are unilateral, and the opposite lobe may be uninvolved, we believe now that a total thyroidectomy should be done, probably in all cases. In other words, we want to prepare the patient in case he later develops distant metastatic disease. We also want to prepare him for radio iodine studies later. We can control his thyroid metabolism easily and simply by a few tablets of thyroxine by mouth per day, so that a total thyroidectomy, if we can leave the parathyroids and at least one recurrent nerve, is not too bad a problem for the patient. I think that has been one of the most interesting things that has developed in human cancer material in some time—this demonstration of the redifferentiation towards the normal.

Now there are two changing concepts that are important. One is a somewhat philosophic one and the other has direct practical bearing. One is the concept of field cancerization in the multicentric origin of tumors. This (slide) is an obvious example of such, in a roentgen dermatitis in a man with

multiple changes and multiple carcinomas of the face. He was treated with x-ray for acne in his youth, and you see the late result which is so common. I show him simply as an example of multicentric origin and field cancerization. It is possible that many tumors, particularly in stratified squamous epithelium, arise from a preconditioned field of epithelium and arise in many cells at once.

Here (slide) is an example of a perfectly characteristic early carcinoma of the lateral border of the tongue in a typical location. Here is the tumor that we see clinically. This granular change posteriorly does not look particularly significant, and it might be that it might not be included in the radiation port or in surgical excision. This (slide) is a low power view of that tumor, this is the raised palpable lesion, the obvious cancer that we saw anteriorly. Here is the granular area posteriorly. I want you to pay particular attention to that area which looks somewhat like the boot of Italy. This is a higher magnification of that, and we see it as an isolated focus of cancergenesis arising from an apparently benign overlying epithelial mucosa. You can see carcinoma streaming down from it; that area is surrounded by abnormal but benign epithelium. These other cancer aggregates can be traced on serial sections back to such isolated foci of cancerogenesis. It is an example of multiple origin.

The same thing is true in other areas. Here (slide) is the colon from a man who in 1930 had a posterior resection for carcinoma of the rectum. Later he developed a carcinoma of the splenic flexure, then he developed a carcinoma of his colostomy and finally a colectomy was done and he had multiple carcinomas and polyposis, again an example of multicentric origin. We must keep this in mind in these areas in which we can show such a condition.

In a study of multiple tumors done several years ago, a study of some 1868 instances of multiple tumors, the interesting finding was that the majority occurred in the same organ or pairs of organs. Now that is important.

Skin, of course, is the most common, and skin and lips; colon would be next, and somewhat to my surprise, stomach was more common than I had realized. As to multiple carcinomas of the paired organs, the breasts because of their normal incidence, would be the most common site of bilateral tumors; ovaries are less than you would expect but we all know that bilateral ovarian carcinoma is exceedingly common, but it is not reported because of the possibility of peritoneal metastases from one to the other, where that does not apply in testicular tumors; kidneys we know about—bilaterality there is mainly in children with Wilm's tumors. The concept of the multicentric origin changes somewhat, at least, my intellectual approach to the treatment of these lesions.

Now the second concept that is important, the old teaching that carcinomas metastasize by lymphatics and sarcomas by veins, is not true. Sarcomas do metastasize essentially by the venous system. We know today that many carcinomas metastasize by the venous system, particularly of the breasts, thyroid, kidney, prostate, lungs, etc. But, probably the most common malignant tumor affecting human beings is squamous cell carcinoma; the skin, mucosa of the oral pharynx, metaplastic variants in the bronchi, trachea, nasopharynx, naso-sinuses, urinary bladder, vagina, and cervix are rather common sites, so that I think it is fair to say that squamous cell carcinoma is probably the most frequent form of malignant tumor.

Now this one has a minimal tendency to metastasize by vein. That is important because it means that it is a lymphatic metastasizer and is essentially a localized disease. If we can eliminate it locally, it is possible to cure the patient. We do not have the problem, in other words, of disseminated metastases into the liver, lumbar spine, lung, brain, etc. from this tumor that we have in others. We have it, of course, but in no ways near the same percentage, so it allows us an intellectual reason for widening our surgical attack. This has been of greatest benefit in head and neck cancer; and in recent years there has been developed an approach to advanced head and neck cancer which demonstrates that we can salvage a few of these patients.

Here (slide) is an instance of such a situation. This is an excavation of a mandible due to an extensive cancer of the floor of the mouth and tongue extending directly into the mandible. This lesion had had heavy radiation to the maximum point of tissue tolerance. Bone was invaded by direct extension, and of course you can't see them but there were extensive cervical node metastases.

Now with the advent of antibiotics, our better understanding of fluid balance and shock, multiple transfusions and a perfection of tracheal anesthesia, and with the realization that these tumors are lymphatic metastasizers and possibly confined to this area, an operation has been devised to attack this type of problem which isn't new by any means, but which now can be done with a reasonable mortality. That is a combined radical neck dissection with removal of the jaw and the involved soft parts of the mouth in continuity.

The neck dissection consists essentially of removing everything between the skin and scalene

muscles except the carotid arteries and the vagus nerve. The tissues removed from the neck are left attached to the mandible, which is resected with a gigli saw, and the excision made to include any involved tissues of the mouth—even a hemiglossectomy if the tongue is involved although the tongue is not disturbed if not involved in extension of the tumor.

Repair is effected by suturing the buccal mucosa of the raised cheek flap to the medial cut edge of the soft parts, and in this instance again, the tongue, but unless the tongue is involved, it is not disturbed. This re-constitutes the oral cavity and separates it from the neck. The skin flaps are then approximated, using a double row of interrupted catgut—triple or quadruple 0 size in the mouth. The skin flaps are reapproximated over the drains which are placed wherever it is most convenient.

A surgical specimen of such a lesion (shown in a slide) included a deeply excavating ulcerating carcinoma of the floor of the mouth and gingiva; the symphysis and angle of the mandible; submaxillary gland metastatic disease in nodes; the jugular vein, sternomastoid and omohyoid muscles, etc.

That would seem to be an exceedingly brutal operation. It is not nearly as bad from the standpoint of either appearance or function as we expected it to be. Most of these people are in age groups in which function is much more important than appearance, and it is apparent that we can cure, by this means, from the standpoint of a five year salvage free of disease, some of these formerly hopeless problems.

Here (slide) is an old gentleman who was 78. When we first saw him he had a huge carcinoma of the buccal gutter and gingiva; it had ulcerated through the whole thickness of the cheek, fungating out and extending almost to the midline. The commissure of the mouth was involved, bone was involved, and he had massive metastases in the neck. He was a perfectly miserable individual. That type of patient is salvagable and he is much happier. This man was operated upon three and a half years ago. He has gained weight, follows his business, is still active, and is happy about the whole thing. He, I think, is a complete salvage.

This man (slide) was 65. He had had again a carcinoma of the buccal gutter and mucosa which had been treated elsewhere by radiation. The lesion had recurred and he had had maximum radiation to the point of necrosis of the mandible. He had recurrent cancer in an area of early necrosis with massive metastases to the neck fixed to the under surface of the mandible. Bone was invaded in two ways, both from above by recurrent buccal (residual) cancer, and from below by metastatic disease.

He had such a trismus that he had to have a tooth extracted to take liquids. He had been home for a year on morphine, given up as a hopeless problem, with people waiting for him to die. After getting him in better condition by restoring his proteins to normal, getting his K, and C and other vitamins to a normal status—in other words temporarily and artificially bringing him back to a normal physiologic balance—this procedure was done. It is now over five years since his operation and this man is working as a night clerk in a Chicago hotel to this day. So, we can salvage some individuals today whom, as I say, we considered completely hopeless even a few years ago.

We have applied this principle to a few selected cases elsewhere, of squamous cell epidermoid carcinoma. Since we realized that they are not early vein invaders, it is a local problem. Here (slide) is an example, a young man of 29 who came in with a huge carcinoma of the larynx, and bilateral neck metastases. He came in as an emergency, and required a tracheotomy. He almost lost his life before that could be done. The lesion had completely destroyed the thyroid cartilages, the thyroid gland was invaded, the trachea was destroyed. How he had been breathing that long I don't know. He had entirely lost his voice already and almost completely lost his life.

Tracheotomy was done as an emergency measure and he was temporarily salvaged. He was then checked over thoroughly to see if there was clinical evidence of metastatic disease. There was none, and an attempt was done at a bilateral neck dissection, total laryngectomy, total cervical tracheectomy, total thyroidectomy. This was done and was done more extensively than the artist has indicated here. We did the lesser involved side first, and spared the jugular vein, and then we went ahead and completed the other side. This was all done in en blocke dissection. His pharynx was involved and we had to do a partial pharyngectomy along with the laryngectomy, tracheectomy, thyroidectomy and bilateral neck dissection. He had bilateral neck nodes which were involved extensively with metastatic disease. We can't take both jugulars at one time, or at least I wouldn't do it. This operation was done four and a half years ago. This man is working on his farm. He has a good esophageal voice and can carry on a long distance telephone conversation, and so far is entirely well. It is seldom that we can achieve such a result, but in well considered cases, it can be done, and it is reasonable to try in a few of them, and this sort of thing keeps us trying. This is by no means the usual result; it is

unusual and lucky, but it does serve to keep us working at it.

Carcinoma of the esophagus is another area of real surgical advance. This (slide) shows a lesion in the lower cervical esophagus. I think today that we have a better chance of cure of cervical esophageal lesions than we have of thoracic, at least of the upper and middle thirds of the thoracic esophagus. The reason for that is that in the thorax, we are confined to tubular dissection for excision of the esophagus. We cannot go widely laterally and take adjacent structures as we can in the neck. We can't take aorta and heart, etc. In the cervical esophagus, however, we can, we can take trachea, larynx, thyroid, bilateral neck dissection if it is necessary. So theoretically we have a better chance here than we have in the thoracic area.

We haven't done much about this until recently when two ways of reconstructing the patient's physiology have been devised. Watson and Wookey at about the same time devised a flap method of reconstructing the cervical esophagus which is quite satisfactory, and of course in recent years, we are bringing the stomach up through the diaphragm, right into the neck, even to the pharynx if necessary and doing an esophago-gastrostomy in the neck. That is feasible and can be done and is one of the more recent approaches to this problem.

We are doing another thing for lesions of the upper third, which is, to my mind, the worst problem; we are resecting if possible, and then bringing the stomach up, and moving the lower esophagus up into the neck and doing a Wookey, for lesions which would not ordinarily be thought suitable for such a procedure. Again that is squamous cell epidermoid carcinoma, and we are more justified in extending our methods of surgery.

One of the most common of malignant tumors is cancer of the cervix. That again is epidermoid carcinoma, and it has been demonstrated that in a reasonable percentage of patients, at autopsy (which is as advanced as cervix cancer can get) it is confined to the pelvis. Again, it is not a vein invader. It is a lymphatic metastasizer and most of these women die from uremia, both ureters involved by cancer on either side.

Now there has been a significant increase in the surgical treatment of cervical cancer in recent years. I am not going to go into that, but from the standpoint of this concept that I have mentioned of the behavior of squamous cell cancer limiting itself to metastasizing by the lymphatics, Brunschwig has devised a radical procedure which is a combined abdominal-perineal resection of the uterus, rectum, bladder, vagina and so forth in one stage with both ureters being transplanted into the sigmoid.

This operation is only applicable in a limited group. Where the carcinoma of the cervix recurred after adequate radiation, and has produced, by cancer, a vesico-vaginal fistula, and a recto-vaginal fistula, the situation is hopeless from any other standpoint, and if the disease is confined to the pelvic area, theoretically it is possible to cure the patient by such a procedure. It is a radical approach but today it can be done with a fairly reasonable mortality rate.

Now I am not at all certain that this will ever become a standard part of our surgical repertoire. I am not at all satisfied with the procedure in my own hands. It is entirely an experimental procedure and I think that we should consider it as such until a great deal more work has been done in evaluation. I don't think there is any more than a three year survival yet, the mortality rate runs around 25 per cent, and even with this physical situation the indications should be limited, at least in my mind, also by the patient's psychologic point of view. There are very few patients who can take this sort of thing postoperatively, if they survive, and it may well be that the living fate is worse than death. This operation has facetiously been called the "All-American;" if we divide this into a "North American" and "South American," then I think we have something. A "South American" would be a situation where a carcinoma of the cervix has invaded the rectum. No general surgeon today hesitates to remove the rectum, vagina and uterus in doing a combined abdomino-perineal resection for carcinoma of the rectum. I don't see any reason why we shouldn't do it from the reverse. Carcinoma of the cervix invading the rectum will kill a patient just as dead as carcinoma of the rectum invading the cervix. I think that is a perfectly reasonable procedure, and I am sure that most surgeons agree. That leaves a patient with a colostomy and a normal bladder sphincter function.

Now the "North American" is the reverse of that where anterior lip cancer has invaded the bladder. If it has gone through the wall, or almost through, that patient is due to have a permanent vesico-vaginal fistula whether she is treated or not. If it is untreated, the tumor will go through. If it is treated by radiation, and cancer has replaced this barrier, it will destroy it, and you will probably have an irreparable vesico-vaginal fistula. There I think the compromise is radical panhysterectomy, vaginectomy as much as necessary and cystectomy and urethrectomy with transplant of the ureters into an intact colon. That preserves sphincter function and is the most satisfactory of the three possibilities; I have a number of happy women who have had that done.

One last word, which not necessarily germaine to this discussion, is one of my particular interests on parotid tumors. I base this on my opinion that the average patient in America today, with a parotid tumor, statistically hasn't a very good chance to get over it. We tend to take these tumors and neck lesions not too seriously, and we don't realize that benign mixed tumors can, if they are left alone long enough, or fooled with often enough, become malignant.

Even in advanced cases, there is a chance of salvaging some of these people. Here (slide) is an example of a mixed tumor of 45 years duration, operated on twice, the last time 15 years ago, and I think it is, without any question, an example of malignant transformation of a mixed tumor. This tumor started to grow rapidly after 45 years; and it had been stationary for 15 years and reached this size in the period of six months. Now a point about these massive parotids that is new to me. This man has an intact facial nerve, much to my utter amazement, and that means the tumor is operable, because it is that point which makes a parotid inoperable. All of this is just external—you can chop it off with a hatchet—the point that makes it inoperable is right back here; and if the facial nerve is intact, it is operable.

This is a tenth day postoperative picture. The jaw was involved so that the mandible had to be removed, and a skin graft was placed. He is well so far, only eight months.

I show you this (slide) as an example of what some of these mixed tumors will do if you don't handle them correctly in the first place. Here is another example of a man of 45 who had had a mixed tumor removed three times, diagnosed by good pathologists and then the last of the three times was carcinoma. He had had irradiation, surgery, irradiation, surgery and finally ended up in this situation. I kept him around a few days in the clinic just to scare the students until one of them pointed out to me that his facial nerve was intact. And, much to my surprise, it was, which meant that it was operable.

It was removed and that was four and a half years ago. This man is still all right so far. He had cervical node metastases as did the preceeding one, and a radical neck dissection was done in continuity with the massive excision. Now this man incidentally was an expert furniture refinisher who had given up his job when he came into the clinic in that condition. Afterwards I got him a job with another expert furniture refinisher who has since died of lymphosarcoma.

To summarize, I have tried to go over some of what I consider to be significant recent advances in cancer therapy; in surgery we do have some justification in a few fields for extending our limits of resection. Sometimes I think that all we have done is to "go an inch wider," but with some thoughtfulness, I think we can justifiably extend our limits of excision.

AMERICAN CANCER SOCIETY
RESEARCH
EDUCATION
SERVICE

Alleviation of Cancer Pain

Eldridge H. Campbell, Jr., M.D., and Robert D. Whitfield, M.D.*

Albany, New York

It was not without good reason that our forefathers termed malignant disease Cancer—the crab. Of its many hideous features, the inexorable spread, the unsightly tumefaction, the erosion, the derangement of function, the wasting and ultimate death, none are more justly dreaded than the pain. There are a few adult patients who do not suspect, or sooner or later realize, their correct diagnosis. No matter how brave nor how well prepared we are philosophically to come face to face with the Grim Reaper, there are few, if any, of us occidentals who can do so without a few qualms. The watches of the night become long indeed.

The ideal control of pain consists in the elimination of its cause. While a surgeon may remove the primary tumor, the painful metastases but rarely lend themselves to such direct attack. On a few occasions solitary metastases have been excised from the brain or lung with more than fleeting relief. Secondary tumors from the prostate may be held in abeyance from a few months to several years by castration or by estrogen therapy; a number of secondary breast tumors have responded temporarily to testosterone or even to the estrogens; a few thyroid metastases have been benefited for a time by radioactive iodine. Nitrogen mustard has proved advantageous in certain cases of Hodgkin's disease, lymphosarcoma and leukemia. The benefits are usually temporary, but may be quite dramatic. Of nine lymphomas followed on the oncology service at the Albany Hospital, five were completely relieved of their back pain for four to six months while two others were partially relieved. A few surgeons have reported its transient benefit to certain metastatic lesions.

Irradiation offers much to certain types of metastatic tumors. In general, the more anaplastic, the less differentiated or embryonically younger the cell, the more likely is it to respond to deep x-ray therapy. Some of the lymphoid group of tumors shrink quite well, while carcinomas of the cervix and body of the uterus may be arrested for long periods. In the brain the medulloblastoma and certain pituitary adenomas may be checked for a good while. On the other side of the ledger are many more malignancies whose responses to irradiation are negligible or fleeting. These are the well differentiated tumors and unfortunately include most of such common new growths as the gastrointestinal, the pulmonary, and the malignant gliomas. When the microscope discloses a type of cell such as carcinoma of the stomach known to be refractory to x-rays, it is open to question whether or not the risk of adding radiation sickness to the patient's woes is worth the gamble. There comes a time when one's card is up, when it is more profitable to adjust oneself to the inevitable than to waste precious physical and financial reserve on frenzied efforts at reversing Fate's irreversible decision.

From this point to the end of the downhill road, it is well to recall that the doomed suffer not only physically but mentally. Much can be done to mitigate these hardships. If the patient can look upon his physician as a friend, stalwart, true and sympathetic, cheerful, yet avoiding false hopes, frank yet diplomatic, conservative regarding further curative measures, yet constantly seeking to improve his welfare, then will his peace of mind and body be gratefully increased. How pertinent was Samuel Johnson's remark: "It is an alleviation of misery not to suffer alone."

Should one tell the patient that he has cancer? That, in our opinion, depends entirely upon the person and his or her circumstances. We as physicians draw back from hurting or in some cases actually crushing the patient by notifying him of his doom. If, by diplomatic dodging of the awful question, we may let a little more sunlight fall in this vale of tears, why not do so? On the other hand, there are some patients so constituted that they demand the truth at once, and others who for financial or other mundane reasons must be warned of the imminence of their departure. In this case complete frankness is not only necessary but a kindness which seldom goes unappreciated.

Two types of palliative operations on cancers no longer curable are frequently worthwhile, are quite familiar, and are mentioned here merely for the sake of completeness. First is the removal of a fungating or ulcerating primary growth, when feasible, even after metastases have occurred, which has been often advantageous at least temporarily from the standpoint of morale, of unsightliness, of odor and of pain. Second, obstruction of the alimentary or urinary tract can oftimes be relieved by operative procedures which in this era are relatively simple, and may well repay the effort. Thus, a gastroenterostomy, an enteroenterostomy, an enterocolostomy or a transurethral resection of the obstructing portion of a

*From the Department of Surgery, Albany Medical College.

**Illustrations published originally in Surgical Clinics of North America.

malignancy may obviate one of the least pleasant modes of finishing our course.

Analgesia by Drugs

In most cases one eventually comes to lean on drugs for pain relief. Of these, opium in some form or other is our chief prop, and, as Dr. Osler remarked in his own last illness, "It is God's own medicine." However, the perfect sedative has not yet been found. Increasing tolerance and unpleasant side reactions are all too frequently encountered. In some individuals, particularly those cursed with severe nerve root involvement, the control of pain by present day analgesic drugs leaves much to be desired. Alcohol, an excellent analgesic and sedative, is, alas, seldom well tolerated by the patient with advanced malignant disease. When it can be taken, its frequent use should be encouraged. Its administration by intravenous infusion is sometimes advantageous.

Intrathecal injection of alcohol was introduced by Dogliotti in 1931. The method is sometimes applicable to cancer pain in the pelvis and lower extremities. With the patient on her side one or two cc. of 95 per cent alcohol is injected into the lumbar subarachnoid space as near the principally involved roots as possible. Since alcohol rises, the side in which most pain is located is placed uppermost, and the patient left thus for one or two hours. Slight burning and paresthesias are often followed by prompt relief of pain on one side. If necessary the injection may be repeated on the other side in a day or two. The procedure is simple and can be carried out on the ward or even in the patient's home. Unfortunately, the method has a number of serious drawbacks. Weakness of the legs and sphincters not infrequently results. Under certain circumstances this may be accepted as part of the calculated risk, provided members of the family understand fully.

The greatest shortcoming of the method is its unreliability in achieving lasting relief. Although all but one of our 26 patients with metastases in the lumbar spine and pelvis obtained immediate respite, in but 12 was this benefit of more than 48 hours duration. More alcohol increases the likelihood of relief but also of motor and sphincter disturbance. Should the patient already be bedridden, and particularly if the tumor itself has brought about the aforementioned neurologic changes, there is no reason why larger amounts of alcohol should not be employed to ease the Crossing of the Bar.

Dorsal Rhizotomy

If cancer pain be limited to a few dermatomes, either unilaterally or bilaterally, and if there is reason to believe that it will not spread elsewhere for some time, it is sometimes profitable to divide the sensory nerve elements intradurally, thus relieving the pain without loss of movement. Inoperable carcinomas of the mouth, throat, sinuses and nasopharynx lend themselves admirably to this procedure, particularly if unilateral. Face and pharynx can be rendered anesthetic by sectioning the trigeminal and glossopharyngeal nerves, and should there be an overlap into the neck the upper cervical roots may be readily sectioned at the same sitting.* The senior author had occasion to review 50 odd such cases of his own and Dandy's. There were no operative deaths, and the relief afforded was greatly appreciated by both the patients and their families.

A few bronchogenic and breast carcinomas involve one or occasionally both brachial plexuses with resultant pain which is all but unbearable. Division of the plexus in the neck can be done easily but since some of the nerves may be involved within the intervertebral foramina, this procedure will not surely stop the pain. The sensory roots may be divided intradurally, sparing the motor fibres. It is advisable to extend the denervation well wide of the present pain and, of course, there is no knowing when a distant nerve involvement may occur. In nine patients upon whom we have performed this operation the results were satisfactory (up to several months) in seven, but only for a few weeks in two. In neither of the latter had we extended the denervation sufficiently wide of the pain.

Chordotomy

Within the spinal cord fibres carrying pain run upwards in a relatively small bundle in the anterolateral quadrant. Temperature fibres lie hard by, while pain, touch, and proprioception are far removed. The large crossed pyramidal tract lies posteriorly and can usually be avoided by keeping the incision anterior to the meridian of the dentate ligament (Figure 1). The advantage of chordotomy over rhizotomy lies not only in the ease with which

*In our experience it has been necessary to divide the trigeminal root completely rather than subtotally to relieve cancer pain. Tic pain will usually be stopped by subtotal division at the pons.

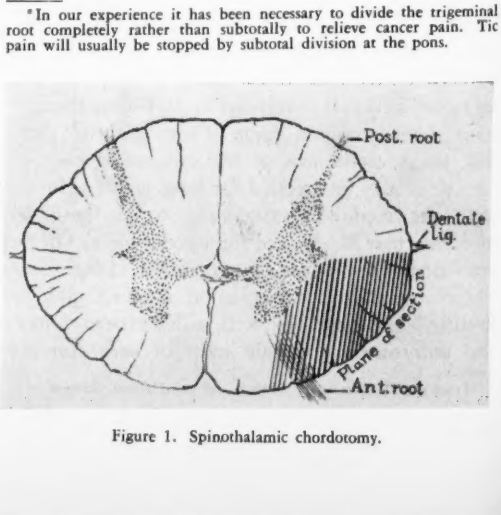

Figure 1. Spinothalamic chordotomy.

it may be carried out but in the much wider areas that may be rendered analgesic. It is of particular value when pain is unilateral and is below the arm level. Here pain relief without serious leg or sphincter palsies may be expected.

The shortcomings of the procedure are, in our hands at least, that cuts made sufficiently deep to secure high levels of analgesia *bilaterally* almost universally result in crippling losses of leg and sphincter power. Should the cancer itself have already brought these changes about, then there is all to gain and little to lose by the procedure.

On the brighter side of the ledger are the reports of White and of Kahn and others in which considerable success has undoubtedly been achieved, particularly when the operation was performed in two stages. It should be noted, however, that many of their patients were suffering from pain not due to malignant disease and therefore by no means so intractable.

Lobotomy

The perception of pain depends not only upon an intact sensory pathway, but upon conscious attention to the sensation. It is probable that the thalamus registers the former while the cerebral cortex is essential for the latter. Animals deprived of cerebral cortex react quickly to painful stimuli as long as the thalamus is intact, while man himself can still perceive pain after the sensory cortex has been destroyed. On the other hand, lesions in certain cortical areas, particularly in the frontal lobes, divert attention to such a degree that pain is but briefly noticed and immediately forgotten. Who has not returned from an exciting hunt or fight and discovered cuts or bruises he did not recall sustaining?

In 1937 Freeman and Watts noted that a patient who had undergone prefrontal lobotomy for mental illness was coincidentally relieved of a previously painful disorder. Thereafter the procedure has been carried out many times for a variety of intractable pains. Our concern today is its effect on cancer pain, a problem quite different from that of phantom limb and indeed of other neuritic and neurotic pains. As mentioned above the two most disturbing features of cancer pain are the prolonged and increasing severity and the inevitable emotional underlay, self-limited only by death.

What may be expected of prefrontal lobotomy? At best the patient will display little outward awareness of his pain, may exhibit little in the way of personality change and, ideally to our way of thinking, become relatively devoid of worry and apprehension. Opiates can usually be stopped at once and without symptoms of withdrawal. Of the 29 cases in which the authors have performed this operation (Figure 2) for cancer pain, 22 were relieved of pain for the one week to 18 months they survived. At the suggestion of Scarff we have performed unilateral lobotomy on the non-dominant side in nine cases with immediate good results in all but early recurrence of pain in six. While the likelihood of profound personality changes and of lasting sphincter disturbance is definitely less in the unilateral group, we believe that in most instances it is more advantageous to carry out bilateral lobotomy at the first operation.

Admittedly lobotomy is accompanied by some risk in any patient in the last stages of cancer. One of our patients with multiple myeloma died of hemorrhage postoperatively. Such an outcome is regrettable but under such circumstances hardly to be regretted. Providing the family understands clearly beforehand what may be expected, most of those who have suffered long and hopelessly with their loved one will and do welcome any form of mental and physical relief.

Summary

Pain of cancer no longer operable is inevitably intensified and colored by the patient's knowledge or suspicion of his diagnosis. Metastases from prostatic carcinoma may be held in check months to years by castration or by appropriate hormone therapy; certain breast cancers have responded similarly. A few thyroid malignancies have been arrested for a time by radioactive iodine. Certain

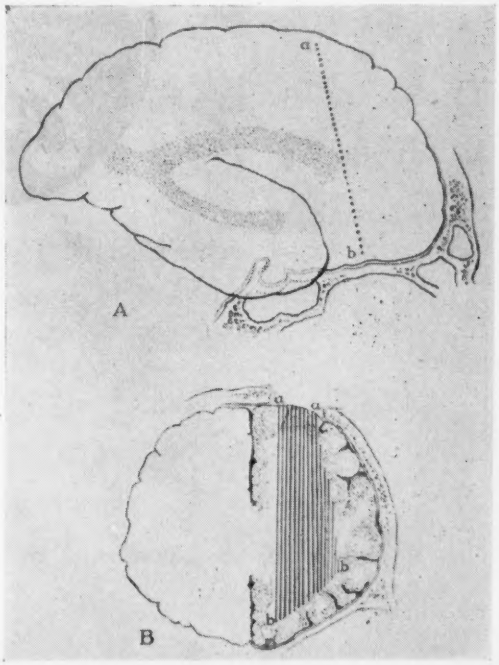

Figure 2. Prefrontal lobotomy.

anaplastic cancers respond favorably to irradiation, occasionally for long periods of time. Nitrogen mustard has been very helpful in certain lymphoid malignancies. For the great majority of inoperable cancers physical relief must be supplied in the form of analgesics and spiritual succor by a wise and sympathetic physician. In those instances in which opiates no longer abolish pain, surgical denervation of the area or prefrontal lobotomy has considerable to offer. At best, however, any or all of these present methods afford alleviation rather than complete relief.

Professional Film Loan Library

Professional films on cancer are available on a free-loan basis to professional groups for showing in connection with meetings in which cancer may be discussed.

These groups may be hospital staffs, medical schools, nursing schools, postgraduate courses in cancer, and state and county medical society meetings.

You are invited to write the Kansas Division, American Cancer Society, 506 New England Building, Topeka, for a catalogue which describes the complete series of films available.

Most of the films, particularly those describing techniques in surgical and radiological procedures in therapy and management, are sent directly from the national office of the Society. At least two weeks should be allowed to clear reservations on these films.

A few of the films are available directly from the state office of the Kansas Division, and are therefore more immediately accessible. This list includes:

ACS-1 Cancer: The Problem of Early Diagnosis

ACS-2 Breast Cancer: The Problem of Early Diagnosis

ACS-3 Breast: Self Examination

ACS-4 Gastro-Intestinal Cancer: The Problem of Early Diagnosis

ACS-N-1 What Is Cancer? (For Nurses)

R-1 Radiotherapy—High Dosage Treatment (For Nurses)

Kansas Division, American Cancer Society

President, Orville R. Clark, M.D., Topeka
Vice President, Mrs. Tom Stewart, Wellington
Chairman, Executive Committee, W. Laird Dean, Topeka
Secretary, J. W. Kirkpatrick, El Dorado
Treasurer, J. D. Bjorkman, Kansas City
Executive Director, Harry M. Dawdy, Topeka

Executive Committee
Kansas Division, American Cancer Society

W. Laird Dean, Topeka, Chairman
John T. Andrews, Lawrence
C. H. Benage, M.D., Pittsburg
J. P. Berger, M.D., Wichita
J. D. Bjorkman, Kansas City
Mrs. W. C. Cavert, Independence
Orville R. Clark, M.D., Topeka
David S. Jackman, Wichita
Mrs. J. E. Johntz, Abilene
Mrs. L. W. Kesler, Winfield
J. W. Kirkpatrick, El Dorado
Charles H. Miller, M.D., Parsons
C. C. Nesselrode, M.D., Kansas City
Robert H. Riedel, M.D., Topeka
Arthur Saville, Topeka
Howard E. Snyder, M.D., Winfield
Mrs. Tom Stewart, Wellington
Robert E. Stowell, M.D., Kansas City
Karl E. Voldeng, M.D., Wellington
Mrs. John Wallace, Colby

Committee on Control of Cancer, Kansas Medical Society

J. P. Berger, M.D., Wichita, Chairman

H. O. Bullock, M.D., Independence

O. R. Clark, M.D., Topeka

A. A. Fink, M.D., Topeka

L. F. Glaser, M.D., Hutchinson

J. J. Hovorka, M.D., Emporia

W. J. Kiser, M.D., Wichita

M. V. Laing, M.D., Kansas City

R. H. Maxwell, M.D., Wichita

C. H. Miller, M.D., Parsons

O. F. Prochazka, M.D., Liberal

R. H. Riedel, M.D., Topeka

C. D. Snyder, M.D., Winfield

R. E. Speirs, M.D., Dodge City

R. E. Stowell, M.D., Kansas City

G. M. Tice, M.D Kansas City

L. E. Vin Zant, M.D., Wichita

K. E. Voldeng, M.D. Wellington

Editorial Board, Journal

Lucien R. Pyle, M

John W. Cavanau

Orville R. Clark, I

Richard Greer, M

Dwight Lawson, I

DATE DUE

WHY CANCER EDUCATION?

Dear Doctor:

There are many health and welfare problems which remain unsolved in spite of the spectacular advances of the medical sciences in the past 50 years. In fact, these advances have created some new problems, the solutions of which lie largely in the field of social action. Cancer can be considered to be in this class.

Our medical advisors tell us that while cancer is generally fatal if untreated, or if treated too late, the fact is that cancer is among the most curable of the major causes of death if treated in time. Medical statistics show that when cancer is properly treated while confined to the breast, 80 per cent cures (five-year survivals without evidence of disease) are possible—yet we are curing only 30 per cent of breast cancer. When cancer of the uterus is treated early, 70 per cent can be cured—yet we are curing only 20 per cent of uterine cancer. When cancer of the larynx is treated while the disease is confined to one vocal chord, it can be cured in 75 per cent of the cases—yet we are curing only 15 per cent.

The reason for this dramatic differential is not that the medical profession lacks the technical ability, but that delay between the appearance of cancer's symptoms and the institution of treatment has prevented application of that ability. This delay is primarily attributable to the patient himself, because it is he who first becomes aware of the trouble and who must take the first step.

The average patient with cancer of the larynx delays 3½ months after he becomes hoarse before he asks his doctor to help him. Men with cancer of the bladder wait five months after appearance of blood in the urine before seeking professional opinion. Similar delays are identified with every found cancer, even that of the skin.

The reduction of this critical delay is the objective of cancer education. It is clearly each individual's own responsibility to know the more common early signs and symptoms of cancer, and to know the pristine importance of action when they appear.

The foregoing suggests that motivation of the patient to take the first step is in the area of social action, a field in which the American Cancer Society has demonstrated its competence. It is for this reason that we consider ourselves to be partners with you in utilizing our present knowledge of the cancer problem.

We covet your continuing cooperation.

Sincerely yours,

Kansas Division,

American Cancer Society, Inc.